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Global excellence in cardiovascular medicine: Central and South America

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Global excellence in cardiovascular medicine: Central and South America

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Editorial: Global excellence in cardiovascular medicine: Central and South America

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Editorial on the Research Topic
Global excellence in cardiovascular medicine: Central and South America

In the last decades Central and South America have experienced rapid changes in lifestyle resulting in a higher burden of cardiometabolic risk factors and a greater contribution of non-communicable diseases to mortality and morbidity (1). Recently, the results of a large prospective study conducted in South America showed that over two-thirds of deaths in the region were due to either cardiovascular disease (CVD), cancer, or respiratory diseases. Only modest differences in the incidence of CVD were observed between countries (2). In all countries, men experienced higher rates of CVD and death compared with women. Deaths were also consistently higher in rural areas across all countries. Incident CVD was largely attributable to 12 modifiable risk factors, with metabolic risk factors being the most prevalent. The largest population-attributable fractions (PAF) for CVD were hypertension, smoking, and abdominal obesity. Outdoor air pollution, an important risk factor for CVD (3), was not included.

The present issue of Frontiers in Cardiovascular Medicine focuses on Latin America and publishes eight articles from groups working in Brazil, Chile, Colombia, and Peru.

Hypertension is the risk factor more studied and sought from different points of view by the Latin American researchers. Amorim et al. compared the sociodemographic, therapeutic, and anthropometric characteristics of 2.956 Brazilian hypertensive patients attending public and private centers, which showed 67.8% of uncontrolled hypertension in the public centers with some improvement in the private centers (47.6%). These data are similar to those previously reported for all South American countries (4). These results highlight the need to implement new strategies to improve hypertensive control in the region as demonstrated by a community-based comprehensive intervention (5).

As Latin America is a region of enormous geographical and ethnic differences, with the countries in the Southern Cone experiencing different seasons, Barbosa et al. reviewed the impact of seasonal variations of blood pressure on hypertension phenotypes and the role of air pollution, latitude, and altitude. The authors conclude that in general, but particularly in our region, cohort studies with large samples that include populations with different socio-economic, ethnic and cultural backgrounds are lacking to explain the crucial relationship between environmental factors and hypertension. This definition is important because it has been reported that in

Afro-descendant individuals the higher prevalence of hypertension is mediated by the level of education, a parameter indicator of socioeconomic status (6).

Lanas et al. in Temuco, a Southern Chilean city with elevated levels of air pollution using wood as a combustible during the cold season, reported that the season of high air pollution was associated with increased cardiometabolic risk factors and estimated cardiovascular risk, regardless of the lower levels of circulating acute inflammatory molecules. This contradiction is explained by the authors as the presence of additional causal factors related to lifestyle during the cold season. Public health policies to control air pollution and improve the control of traditional risk factors should be implemented to reduce the significant increase in cardiovascular events during the cold season.

Hypertension is an important risk factor for cerebrovascular disease (7). Measurement of intracranial pressure may be useful in evaluating the ability of cerebral autoregulation and vascular barriers to protect the brain. Costa et al. presented interesting results of measuring intracranial pressure waveform in 391 long-term essential hypertensive patients with a new non-invasive device that could detect and monitor nanometric skull bone displacement for each cardiac cycle. Normal intracranial pressure was observed in 21.7% of patients, intracranial compliance disorder in 32.7% and intracranial hypertension in 45.6%. These results suggest that the non-invasive device developed and validated by the authors is a safe and precise measurement of intracranial pressure that could contribute to a better understanding of the brain damage induced by hypertension.

Guimaraes Filho et al., presented results showing that in 59 patients the treatment of hypertension guided by central pressure reduction goals, rather than peripheral blood pressure measurement was not able to demonstrate differences in outcomes related to pulse wave velocity and target organ damage, but showed superiority in reducing central diastolic pressure and AIx behavior at the end of a one-year follow-up, opening the possibility that longer follow-ups and greater sampling power may demonstrate the benefits of this treatment strategy.

Pereira et al. evaluated the best cutoff SAGE score, a score based on four clinical parameters (peripheral systolic blood pressure, age, fasting glucose and glomerular filtration rate), that would indicate the risk of a pulse wave velocity $\geq$10 m/s, a predictor of cardiovascular events, in 212 Brazilian hypertensive patients. The best SAGE score was $\geq$7 which is a good predictor and a useful tool for the identification of Brazilian hypertensive patients with elevated pulse wave velocity.

The article by Lopez-Lopez et al. contributed to resolving an old controversy about the waist circumference cut-off point that best identifies the risk of major cardiovascular events (MACE) and incident diabetes in Colombia (8, 9). Data from 6.580 participants in the PURE study cohort were analyzed, after a mean follow-up of 12 years. There were 635 cases of MACE and incident diabetes. A cut-off of 89 cm for men and 86 cm for women are the more sensitive values to identify elevated risks of MACE and incident diabetes. These values were associated with a 1.76-fold and 1.41-fold increased risk of presenting the composite outcome in men and women respectively. The authors suggest using these cut-off points to assess cardiovascular risk in Latin America, but we are expecting the report that includes the other South American countries participating in the PURE study to see if these cut-off points are similar throughout the region, considering that lifestyle changes have started at different times in these countries and considering the important ethnic differences that exist.

Finally, Velarde-Acosta et al., reported the case of a 54-year-old female patient with Takotsubo syndrome (TTS), a rare cardiomyopathy whose pathophysiology is probably linked to an excess of catecholamines causing cardiac stunning and transient ventricular systolic dysfunction. Initially the patient was admitted to the emergency service due to very severe oppressive chest pain associated with nausea, vomiting and sweating. The ECG suggested an acute myocardial infarction, but the coronary angiography did not confirm this suspicion. Cardiac computed tomography showed an intracavitary mass that supported the hypothesis of a myxoma as a trigger of TTS, which was confirmed after the removal of the tumor. The patient remains asymptomatic at 6 weeks of follow-up.

We believe that this issue of Frontiers in Cardiovascular Medicine dedicated to Latin American countries is a good representation of the research that is developing in this area. However, we think that there is much more academic production and that we must insist on inviting our colleagues to participate in this initiative that gives visibility to our work and contributes to define the best strategies to improve the control of the principal risk factors in our region.

Author contributions

PL-J: Writing – original draft, Writing – review & editing.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Seasonal variation in blood pressure: what is still missing?

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Seasonal variation of blood pressure (BP) is a topic in cardiology that has gained more attention throughout the years. Although it is extensively documented that BP increases in seasons coupled with lower temperatures, there are still many gaps in this knowledge field that need to be explored. Notably, seasonal variation of BP phenotypes, such as masked and white coat hypertension, and the impact of air pollution, latitude, and altitude on seasonal variation of BP are still poorly described in the literature, and the levels of the existing evidence are low. Therefore, further investigations on these topics are needed to provide robust evidence that can be used in clinical practice.

KEYWORDS

blood pressure, seasonal variation, masked hypertension, white coat hypertension, air pollution, altitude, environment

1. Introduction

Seasonal variation of blood pressure (BP) is an important topic in cardiology that has gained more relevance throughout the years. In the treatise titled "*On Airs, Waters, and Places*" (1) Hippocrates had already suggested in 400 BC that to investigate medicine properly, physicians should "*in the first place to consider the seasons of the year, and what effects each of them produces*". Rose (2) reported in 1961 the first analysis evidencing the influence of BP fluctuations within the seasons. Since then, several epidemiological studies have shown that cold air stimulation can promote an increase in BP (3–5). Additionally, clinical trials indicated an association between seasons with lower temperature and greater cardiovascular mortality (6, 7). In 2020, the ESH Working Group on Blood Pressure Monitoring and Cardiovascular Variability published a consensus statement on seasonal variation of BP (8) summarizing the main evidence on this topic so far. They described several interesting aspects of the pathophysiological mechanisms involving temperature and BP, different strategies for measuring the seasonal variation of BP, the prognostic relevance of seasonal BP changes, clinical implications of this association, and final recommendations for clinical practice. However, we would like to raise some other important gaps that still need further investigation and may contribute to a better understanding of seasonal BP variation. In this review, we will discuss the existing knowledge and the gaps about the association of seasonal variation of BP with different hypertension phenotypes, air pollution, latitude, and altitude.

2. Masked hypertension and white-coat hypertension

Hypertension is a major risk factor for cardiovascular events (9, 10) and is usually diagnosed based on office BP measurements. However, due to BP variability, current guidelines have recommended the performance of out-of-office BP measurements besides office BP measurements for a more accurate diagnosis of hypertension (11). The evaluation of office and out-of-office BP in the same subject has revealed that different hypertension phenotypes may exist (11). Sustained hypertension (SH) is usually the most common hypertension phenotype and is coupled with elevated cardiovascular risk (11). Masked hypertension (MH) and white-coat hypertension (WCH) must be also considered, given their high frequency in the population and clinical relevance. MH and WCH may have heterogeneous prevalence in diverse clinical settings and populations, reaching 7%–52% and 9%–54% respectively (12, 13). In this regard, a recent study by Barroso et al. (14) evidenced an expressive rate of misdiagnosis when solely regarding on office BP levels. The authors identified that 20.6% of the participants with an office prehypertension diagnosis had MH, while 27.8% of individuals with office stage-1 hypertension had WCH. Importantly, both MH and WCH are also associated with higher cardiovascular morbidity and mortality when compared with normotension (15).

Because both office BP and out-of-office BP increase in colder seasons, the prevalence of SH is markedly greater in the winter when compared to the summer (8, 16, 17). Conversely, little is known regarding the impact of the seasons on MH and WCH. A *post-hoc* analysis of the Japan Morning Surge Home Blood Pressure (J-HOP) Study (16) evaluating 4,267 individuals found that MH prevalence was lower in the summer compared to the other seasons [MH odds ratio (OR) winter/summer = 2.36 [95% Confidence Interval (CI) = 1.79–3.10], $p < 0.001$] while WCH prevalence was higher in the summer, with an OR winter/summer = 0.55 (95% CI = 0.42–0.72; $p < 0.001$). Likewise, an ambulatory BP monitoring study (18) including 1,075 Japanese patients with chronic kidney disease evidenced that MH was more common in the winter, while WCH was more prevalent in the summer. By contrast, a Chinese study evaluating 649 adolescents assessed by ambulatory BP monitoring reported that both WCH and MH were more frequently detected in the summer (17). Furthermore, Narita et al. (19) found a higher prevalence of nocturnal masked hypertension in the summer among 2,544 Japanese individuals assessed by home BP monitoring. The discrepancies regarding the seasonal variation of hypertension phenotypes reported by the aforementioned studies underscore the need of further studies addressing this topic. In addition, available studies were conducted in Eastern countries and it is not known whether their results may be reproducible in other populations.

3. Air pollution

Another important topic is the impact of air pollution on the seasonal variation of BP (20). Both in- and outdoor air pollution are harmful to the cardiovascular system and may increase the BP (20, 21). However, most of the studies on this topic have focused on the short-term effects of air pollution on BP (22, 23). Air pollutants concentration may vary seasonally, depending on the region (24). Thus, some studies reported seasonal differences in the association of air pollution with all-cause and cardiovascular mortality (25–28). Recently, Jin et al. (29) found that environmental ozone was associated with an increased risk of cardiovascular diseases (hazard ratio = 1.0035; 95% CI = 1.0033–1.0037) during the warm months in older Americans.

Air pollutants have been also associated with hospital admissions for hypertension, depending on the climate conditions. Tsai et al. (30) and Chen and Yang (31) found that different air pollutant types were associated with hospitalizations on warm and cool days. Wu et al. (32) conducted a cohort study with young adults and found significant interactions between temperature and air pollution on BP, especially for high air pollution concentrations. The average systolic BP (SBP) change related to a 10°C decrease in temperature for high concentrations of particulate matter with a diameter ≤2.5 μm was 3.6 mmHg (95% CI = 1.9–5.2 mmHg). Similar results were found for organic carbon and nitrogen dioxide, being the average SBP change of 3.3 mmHg (95% CI = 2.0–4.6 mmHg) and 2.8 mmHg (95% CI = 1.6–4.1 mmHg), respectively. A cross-sectional study by Choi et al. (33) also found that summer and winter seasons present correlations of different air pollutants with increased SBP and diastolic BP (DBP) in each season. Fine particulate matter and nitrogen dioxide were associated with BP increase in the warm-weather seasons, while sulfur dioxide and ozone were associated with BP increase in the cold-weather seasons. It is important to note that most of the aforementioned studies were restricted to Easter Asia, which could also limit the external validity of results for other geographical areas with different ethnicities and cultural characteristics. Therefore, further studies about the role and impact of air pollution on BP and its seasonal variability are needed (34).

4. Latitude and altitude

BP may vary differently from geographical areas because of differences in latitude and altitude, given that Earth is a geoid. Few studies evaluated differences in seasonal variation of BP according to latitudes, and most of them assessed the effects of temperature and ultraviolet light (35, 36), as well summarized by Weller et al. (37). Of note, Duranton et al. (35) conducted a study in patients undergoing haemodialysis in different latitudes in Europe and found that individuals on northern latitudes had an attenuated seasonal variation of the BP. Interestingly, the same group (38) found no interaction of different latitudes in the seasonal variation of BP when analysing a different cohort of haemodialysis patients, suggesting that knowledge on this topic is far from be established. It is also noteworthy that a substantial part of the evidence evaluating the impact of latitude on seasonal variation of BP was derived from a specific group of patients (hemodialysis patients) and was conducted in Europe.

Furthermore, there is a lack of evidence regarding the effects of geomagnetic activity and gravity on the different latitudes and how they could affect BP in the different seasons.

Altitude is also known to interfere with BP. Tsao et al. (39) conducted a cohort study in Taiwan with a small sample of subjects comparing BP in different altitudes in winter and summer. SBP showed a significant variation between altitudes in winter (120.4 ± 17.6 mmHg at 298 m vs. 136.1 ± 19.3 mmHg at 2,610 m; $p < 0.0001$), but not in summer (120.7 ± 13.2 mmHg at 298 m vs. 123.6 ± 17.0 mmHg at 2,610 m $p = 0.0786$). However, DBP variation was significant in both seasons (78.1 ± 11.6 mmHg at 298 m vs. 82.6 ± 10.9 mmHg at 2,610 m $p = 0.0096$, and 78.9 ± 8.9 mmHg at 298 m vs. 76.2 ± 8.9 mmHg at 2,610 m $p = 0.0022$, respectively). To our knowledge, this is the only study we found assessing the effects of altitude on the seasonal variation of BP. Therefore, further studies are necessary to establish the impact of altitude on seasonal BP variation.

5. Conclusion

Further investigations are still needed to establish the real impact of seasonal variation of BP on hypertension phenotypes and the role of air pollution, latitude, and altitude on this regard. For all topics, there is an urge for studies with more robust designs—preferably cohorts, using primary datasets (not *post-hoc* analyses), with larger sample sizes, and evaluating broader populations with different ethnicities and cultural characteristics. Hypertension and BP involve the individual's intrinsic and extrinsic characteristics. Genetic propensity combined with behavioral and environmental factors may result in a predisposition to developing hypertension (40). For that reason, it is important to assess different ethnicities (genetic pools), cultures (dietary intake and other behavioral factors), and geographical areas in studies evaluating BP, especially seasonal variations of BP.

As Hippocrates has written in "*On Airs, Waters, and Places*" (1), it is crucial to understand the environmental factors underlying and associated with diseases. In the case of BP and hypertension, the environment plays a very important role, and, once physicians understand better these aspects, patients will be benefited from more individualized treatments and management.

Author contributions

EB conceived the manuscript idea. EB, GF and CB reviewed the literature and wrote the manuscript. WN, AC and MC participated in the design and reviewed the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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Pharmacological treatment of hypertension guided by peripheral or central blood pressure: a comparison between the two strategies

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Background: Arterial hypertension treatment guided by central blood pressures (CPB) rather than peripheral blood pressures (PBP) measurement has the potential to show greater effectiveness in preventing or even regressing stiffness and target organ damage (TOD).
Objective: This study aimed to compare the parameters of CBP and PBP measurements, arterial stiffness, TOD and renal profile in patients with anti-hypertensive treatment guided by CBP or PBP targets.
Methods: A randomized clinical trial was conducted in central group (CG) and peripheral group (PG). Patients were randomized, evaluated every 3 months for BP and antihypertensive adjustments during a one-year follow up. The procedures in V1 and V5: anthropometric assessment; CBP/PBP measurements, carotid ultrasound; echocardiography; laboratory tests. Paired and unpaired *t*-tests and the χ^2 were used (significance level: 5%).
Results: The study evaluated 59 participants (30CG/29PG). The augmentation index (AIx) was higher in the CG (27.3% vs. 20.3%, $p = 0.041$). Intergroup analysis has found central diastolic BP lower in the CG (78.9 vs. 84.3 mmHg, $p = 0.024$) and the AIx difference between groups ceased to exist after a one-year follow-up. Intragroup comparisons, after intervention, showed a lower frequency of changed PWV ($p < 0.001$) and LVMI ($p = 0.018$) in the CG. The PG showed a higher frequency of changed PWV ($p < 0.001$) and LVMI ($p = 0.003$).
Conclusion: The intervention guided by central BP reduced the central diastolic BP and AIx compared to the PG. There was a reduction in the frequency of changed PWV and LVMI in the CG.

KEYWORDS

arterial stiffness, central blood pressure, clinical trial, hypertension, pulse wave velocity

Introduction

Arterial hypertension (AH) is the main modifiable risk factor for cardiovascular disease (CVD) and premature mortality worldwide. It is traditionally diagnosed and treated based on peripheral blood pressure (BP) measurements (1–3).

The incorporation of arterial stiffness measurements into traditional scores for cardiovascular (CV) risk stratification and the early identification of vascular damage significantly improves the prediction of CV events. Pulse wave velocity (PWV) is a well-established measurement, an excellent biomarker that can identify subclinical target organ damage (TOD), and, when increased, is associated with a considerable increased CV mortality in hypertensive patients (1, 2, 4, 5).

The implementation of simplified technology and research on new low-cost methods to measure or estimate aortic stiffness have increased its use in clinical practice. Currently, different validated devices to measure central BP and PWV are available for clinical use (6) and can improve the prediction of a ten-year risk of CVD by 13% in intermediate risk patients (7).

Moreover, the presence of residual CV risk in the hypertensive population, delayed identification of subclinical damage, and implementation of optimized therapeutic strategies may be associated with difficulties in the absolute reduction of CV outcomes. The association of therapeutic strategies based only on peripheral BP measurements with these difficulties has been debated (3, 5, 8).

The hypothesis that the treatment guided by central BP reduction goals may present advantages over the conventional treatment strategy in reducing intermediate outcomes has biological plausibility (9–12). Few studies have tested this hypothesis, but the superiority of central BP parameters over peripheral ones in predicting CV risk highlights the importance of evaluating the possible behavior of some biomarkers such as PWV as risk factors (13–17).

Therefore, AH treatment guided by central BP parameters has the potential to show greater effectiveness in preventing or even regressing stiffness and TOD when compared to the conventional strategy (18, 19).

Thus, the objectives of this study were: (1) to verify if the treatment guided by central BP values has better effects on central BP values, carotid ultrasound, and Doppler echocardiography compared to the treatment guided by peripheral BP values; (2) to compare central BP values, carotid ultrasound, and Doppler echocardiography before and after the study in each of the groups; and (3) to compare inter- and intragroup frequency of changed PWV, left ventricular LVMI, and creatinine clearance.

Patients and methods

This study is an open-label, randomized, clinical trial conducted in two AH reference services. The study protocol was approved by the Research Ethics Committee under opinion no. 2.746.523, and all participants signed the informed consent form before study procedures.

The inclusion criteria were patients with AH, aged 18 years or more, using or not using antihypertensive drugs, and with an indication for pharmacological treatment based on casual BP measurements (1).

The exclusion criteria were patients with end-stage chronic diseases or previous CVD, including coronary artery disease (acute myocardial infarction, angina, coronary artery bypass graft surgery, or angioplasty) or stroke (ischemic and hemorrhagic stroke or transient ischemic attack) less than six months before the study. These criteria were defined by information obtained directly from the patients or from complementary tests.

Study participants answered a sociodemographic questionnaire, had their body mass and height measured to calculate the body mass index (BMI) (20, 21), had their peripheral and central BP measured, and underwent Doppler echocardiography, carotid ultrasound, and laboratory tests.

Peripheral BP was measured in the office, in a quiet and silent environment, using an HEM-1100 OMRON® automatic device and following the recommended guidelines (1, 5). Central BP measurement was performed, under the same conditions, using the Cardios Dyna MAPA AOP® device with the ARV Solver algorithm (three consecutive measurement protocol and C1 calibration) to verify the central BP, PWV, total vascular resistance (TVR), and augmentation index (AIx).

Cardiac and vascular structural damage was assessed by Doppler echocardiography and carotid ultrasound using a TOSHIBA Xsario ultrasound device. The parameters analyzed included the interventricular septum and left ventricular posterior wall, LVMI, and left atrial volume measurement on Doppler echocardiography, and carotid intima-media thickness (cIMT) measurement and carotid plaque search on carotid ultrasound. All tests were performed by the same observer in each of the services.

The definition of cardiac and vascular damage was established using the following biomarkers: IMT >0.9 mm or presence of atherosclerotic plaques in carotid arteries (22, 23), left atrial diameter greater than 38 mm for women and 40 mm for men, LVMI >95 mg/m^2 for women and >115 mg/m^2 for men, and PWV ≥10 m/s (1, 5).

Creatinine was tested for the subsequent calculation of the glomerular filtration rate (GFR) using the Modification of Diet in Renal Disease (MDRD) formula and considering values ≤60 ml/min/1.73 m^2 as reduced (24).

Treatment strategies were similar regarding the drugs used for both groups, and level adjustment was at the investigating physician's discretion to achieve the goals in both groups: level 1—Losartan 50 mg/day; level 2—Losartan 50 mg 12/12 hs; level 3—Losartan 50 mg 12/12 hs + Amlodipine 5 mg/day; level 4—Losartan 50 mg 12/12 hs + Amlodipine 10 mg/day; level 5—Losartan 50 mg 12/12 hs + Amlodipine 10 mg/day + Hydrochlorothiazide 12.5 mg/day; level 6—Losartan 50 mg 12/12 hs + Amlodipine 10 mg/day + Hydrochlorothiazide 25 mg/day; level 7—Losartan 50 mg 12/12 hs + Amlodipine 10 mg/day + Hydrochlorothiazide 25 mg/day + Spironolactone 25 mg/day.

There was no wash-out before randomization (1, 5, 6, 25). It is noteworthy that the use of the same antihypertensive drug strategy for both groups aimed to ensure that the only difference between

TABLE 1 Central systolic blood pressure values according to age categories, for males and females, in the normal and reference populations (25).

	Normal population		Reference population	
	Female	Male	Female	Male
>20	97 (86, 91, 102, 109)	105 (95, 99, 109, 113)	99 (88, 93, 105, 120)	109 (96, 102, 117, 127)
20–29	95 (80, 88, 102, 110)	103 (92, 97, 109, 115)	101 (88, 94, 110, 124)	110 (95, 102, 120, 130)
30–39	98 (84, 90, 108, 119)	103 (88, 95, 112, 120)	111 (92, 100, 127, 141)	114 (95, 103, 129, 144)
40–49	102 (87, 93, 113, 123)	106 (90, 97, 114, 123)	116 (95, 104, 133, 146)	118 (97, 106, 132, 144)
50–59	110 (93, 100, 119, 127)	110 (96, 102, 118, 126)	120 (100, 109, 134, 148)	123 (102, 111, 137, 150)
60–69	114 (97, 105, 122, 129)	114 (97, 105, 122, 128)	128 (105, 115, 141, 154)	128 (105, 115, 142, 155)
70+	118 (100, 109, 126, 131)	116 (99, 107, 124, 130)	138 (113, 126, 152, 164)	135 (113, 124, 147, 160)

Values given here are 50th (10th, 25th, 75th, and 90th) percentiles.

them would be related to the goal guided by central or peripheral parameters.

After the initial visit, the participants were evaluated every 90 days to adjust the drug level. For the CG, the goal was to maintain central systolic BP below the values established with reference to sex and age group (25) (Table 1). For safety, the minimum limit for peripheral BP reduction was 110/70 mmHg.

For the PG, the goal was a peripheral BP value lower than 140/90 mmHg for low and medium risk and lower than 130/80 mmHg for high risk such as European Society of Cardiology and the European Society of Hypertension Guidelines (1, 5).

If the patient did not meet the defined goals in the return visits, the drug level was increased at medical discretion. Patients who did not show up for a visit after at least two contact attempts were considered lost to follow-up.

Statistical analysis

Statistical analysis was performed with the Stata software version 14.0. The Shapiro Wilk test was used to verify the normality of data distribution. Quantitative variable values and deltas were compared between groups at the beginning and end of the study using the unpaired *t*-test for quantitative variables with normal distribution and the Mann–Whitney *U*-test for quantitative variables with non-normal distribution. The χ^2 or Fisher's tests were used to compare qualitative sociodemographic, BP, and complementary test variables; drug level used at each visit; and the frequency of intragroup PWV, ventricular mass index, and creatinine clearance changes at the initial and final visits. The significance level was set at 5% for all tests.

Result

The initial sample consisted of 130 participants, of whom 59 (30 CG and 29 PG) completed the study, with no deaths or serious adverse events. The 71 losses to follow-up (54.6%) occurred due to the coronavirus disease 2019 (COVID-19) pandemic.

At the initial visit, the groups were similar in terms of sociodemographic characteristics, BMI, cardiovascular risk factors, central and peripheral BP measurements, variables obtained by carotid ultrasound and Doppler echocardiography, and GFR. Only the AIx was higher in the CG (Table 2).

No differences were identified in peripheral BP, carotid ultrasound and Doppler echocardiography variables, and in GFR after the 12-month follow-up. Central diastolic BP was lower in the CG than in the PG. The delta also showed a greater AIx and TVR reduction in the CG than in the PG (Table 3).

Central diastolic pressure and AIx were reduced in the CG and AIx was increased in the PG at the end of the one-year follow-up (Figure 1).

The use of three antihypertensive drugs showed a higher frequency than monotherapy and dual combination in both the CG and PG at the initial and final visits. There was no inter- or intragroup drug level difference before and after the follow-up (Table 4).

TABLE 2 Comparison between the central and peripheral groups before intervention regarding sociodemographic variables, body mass index, central blood pressure measurements, carotid ultrasound, Doppler echocardiography, and glomerular filtration rate, $n = 59$, 2018–2020.

Variables	CG ($n = 30$)	PG ($n = 29$)	p
Women	20 (66.7%)	20 (69.0%)	0.850
Age (years)	60.5 ± 9.8	59.1 ± 9.6	0.582
BMI (kg/m^2)	29.2 ± 5.6	30.1 ± 5.2	0.507
Central BP			
Central systolic BP (mmHg)	125.0 ± 14.5	124.0 ± 14.6	0.793
Central diastolic BP (mmHg)	84.4 ± 10.6	86.5 ± 11.5	0.472
Peripheral systolic BP (mmHg)	133.4 ± 15.7	131.2 ± 14.9	0.574
Peripheral diastolic BP (mmHg)	83.5 ± 10.6	85.5 ± 11.6	0.481
Central pulse pressure (mmHg)	39.8 ± 8.8	36.2 ± 8.3	0.112
Augmentation index [AIx(%)]	27.3 ± 12.2	20.3 ± 13.3	**0.041**
TVR	1.3 ± 0.23	1.3 ± 0.20	0.176
PWV (m/s)	8.3 (8.0–10.3)	8.3 (7.7–9.3)	0.495
Carotid ultrasound			
Presence of plaque	14 (46.7%)	11 (37.9%)	0.497
Carotid IMT (mm)	0.8 ± 0.41	1.0 ± 0.23	0.053
Doppler echocardiography			
Interventricular septum thickness (mm)	9.0 (9.0–11.0)	9.0 (8.0–10.0)	0.543
LV posterior wall thickness (mm)	9.8 ± 1.33	9.5 ± 1.38	0.370
LV diastolic diameter (mm)	47.1 ± 4.7	47.4 ± 4.6	0.818
LV mass index (g/m^2)	92.7 ± 27.5	88.9 ± 26.6	0.596
LA volume (ml/m^2)	28.3 ± 6.4	30.0 ± 8.7	0.402
GFR (ml/min/1.73 m^2)	75.0 ± 21.3	76.7 ± 19.9	0.746

GFR, glomerular filtration rate; LV, left ventricle; LA, left atrium; BMI, Body mass index; BP, Blood Pressure; IMT, Intima-Media Thickness.
χ^2; Unpaired *t*-test; Mann–Whitney *U*-test.

TABLE 3 Comparison of absolute values and deltas between the central and peripheral groups after the 12-month intervention regarding central blood pressure measurements, carotid ultrasound, Doppler echocardiography, and GFR, $n = 59$, 2018–2020.

	CG	PG	*p*	CG	PG	*p*
	Absolute values*			Delta*		
Central BP						
Central systolic BP (mmHg)	116.0 ± 2.8	120.0 ± 13.5	0.247	−9.0 ± 17.3	−4.0 ± 17.4	0.273
Central diastolic BP (mmHg)	78.9 ± 9.7	84.8 ± 10.4	**0.024**	−5.5 ± 8.6	−1.5 ± 12.2	0.151
Peripheral systolic BP (mmHg)	124.3 ± 14.1	128.0 ± 15.1	0.334	−9.2 ± 15.2	−3.2 ± 16.9	0.160
Peripheral diastolic BP (mmHg)	78.1 ± 9.8	83.1 ± 10.9	0.069	−5.4 ± 8.1	−2.4 ± 12.5	0.286
Central pulse pressure (mmHg)	36.5 ± 11.6	35.1 ± 9.5	0.624	−3.4 ± 14.4	−1.1 ± 7.9	0.466
Augmentation index [AIx(%)]	23.3 ± 11.0	23.8 ± 11.4	0.876	−4.0 ± 12.1	3.4 ± 12.1	**0.016**
TVR	1.3 ± 0.2	1.4 ± 0.2	0.311	−0.001 ± 0.2	0.13 ± 0.2	**0.038**
PWV (m/s)	8.3 (7.9–9.6)	8.4 (7.6–9.3)	0.785	−0.2 ± 0.6	0.1 ± 0.6	0.061
Carotid ultrasound						
Presence of plaque	12 (60.0%)	9 (47.4)	0.176	–	–	
Carotid IMT (mm)	0.7 ± 0.4	0.9 ± 0.3	0.237	0.06 ± 0.1	0.04 0.1	0.569
Doppler echocardiography						
IV septum thickness (mm)	8.7 ± 1.5	8.7 ± 1.4	0.943	−0.06 ± 0.9	−0.2 ± 0.7	0.108
LV posterior wall thickness (mm)	8.7 ± 1.4	8.8 ± 1.2	0.832	−0.6 ± 1.0	−0.2 ± 0.8	0.185
LV diastolic diameter (mm)	46.3 ± 3.4	45.9 ± 4.1	0.803	0.4 ± 2.1	0.2 ± 1.5	0.750
LV mass index (g/m^2)	78.5 ± 26.9	71.0 ± 18.2	0.319	−1.6 ± 22.0	−8.1 ± 14.3	0.289
LA volume (ml/m^2)	34.3 ± 10.1	33.4 ± 5.8	0.785	3.2 ± 8.5	−0.2 ± 8.0	0.272
GFR-MDRD (ml/min/1.73 m^2)	74.55 ± 24.2	71.93 ± 20.3	0.657	0 -9–7	−5 -13–0	0.302

CG, central group; PG, peripheral group; BP, blood pressure; GFR, glomerular filtration rate, LV, left ventricle.
Unpaired *t*-test; Mann–Whitney *U*-test; Fisher's exact test.

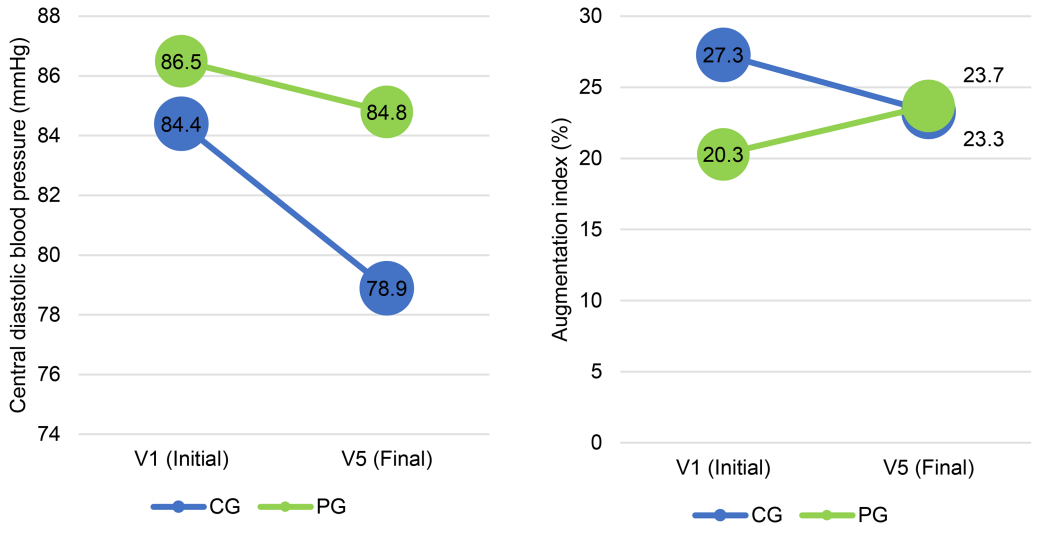

FIGURE 1
Central diastolic pressure and augmentation index values at V1 (initial) and V5 (final) in the CG and PG, $n = 59$. CG, central group; PG, peripheral group.

There was no difference between the CG and PG regarding the frequency of changed PWV values (≥10 m/s), LVMI (>95 mg/m^2 for women and >115 mg/m^2 for men), and GFR (≤60 ml/min/1.73 m^2) at the initial and final visits (Table 5).

When intragroup comparisons were made before and after the intervention, the CG showed a reduced frequency of participants with changed PWV ($p < 0.001$) and LVMI ($p = 0.018$). In the PG, the frequency of participants with changed PWV ($p < 0.001$) increased and of those with changed LVMI reduced ($p = 0.003$). The CG ($p = 0.004$) and PG ($p = 0.004$) showed increased frequency of changed GFR (Table 6).

Discussion

Our study shows that the intervention guided by central BP reduced central diastolic BP but not central systolic BP, and corrected the AIx parameter after a one-year follow-up compared

TABLE 4 Comparison of the number of drugs used before and after the intervention in the central ($n = 30$) and peripheral ($n = 29$) groups.

	Central group ($n = 30$)	Peripheral group ($n = 29$)	p (between groups)
Initial visit			0.222
Monotherapy	3 (10.0%)*	8 (27.6)*	
Double combination	9 (30.0%)*	7 (24.1%)*	
Three or more antihypertensives	18 (60.0%)#	14 (48.3%)#	
Final visit			0.111
Monotherapy	3 (10.0%)*	9 (31.0%)*	
Double combination	9 (30.0%)*	5 (17.3%)*	
Three or more antihypertensives	18 (60.0%)#	15 (51.7)#	

Comparison of intragroup treatment level at the initial and final visits: different symbols indicate statistical difference ($p < 0.001$).

TABLE 5 Comparison of the frequency of pulse wave velocity, left ventricular mass index, and glomerular filtration rate changes between the CG and PG before and after the study.

Variables	CG ($n = 30$)	PG ($n = 29$)	p
Initial visit			
PWV	8 (26.7%)	3 (10.3%)	0.108
LV mass index	10 (33.3%)	7 (25.0%)	0.486
Glomerular filtration	5 (17.2%)	4 (13.8%)	0.717
Final visit			
PWV	4 (13.3%)	4 (13,8%)	0.959
LV mass index	1 (5.3%)	2 (10.5%)	0.547
Glomerular filtration	8 (27.6%)	6 (20.7%)	0.539

Fisher's exact test.

TABLE 6 Comparison of the frequency of pulse wave velocity, left ventricular mass index, and glomerular filtration rate changes before and after the follow-up.

Variables	Initial visit	Final visit	p
CG			
PWV	8 (66.6%)	4 (33.4%)	<0.001
LV mass index	10 (90.9%)	1 (9.1%)	0.018
Glomerular filtration	5 (38.5%)	8 (61.5%)	0.004
PG			
PWV	3 (42.9%)	4 (57.1%)	<0.001
LV mass index	7 (77.8%)	2 (22.2%)	0.003
Glomerular filtration	4 (40.0%)	6 (60.0%)	0.004

Fisher's exact test.

to the group guided by peripheral BP. Intragroup analysis showed a significantly reduced frequency of changed PWV and LVMI in the group of intervention guided by central BP.

This sample included hypertensive patients with a mean age of 60 years and mean BMI of 30 kg/m^2 with well-controlled BP levels in the initial phase of the study. In addition, the comparative analysis in relation to the baseline characteristics showed that the groups randomized to treatment guided by central or peripheral pressure were similar, except for the AIx parameter, which was higher in the CG. As for the antihypertensive drugs used in our clinical trial, all patients used the same strategy in both groups to eliminate potential confounding factors that could occur in the case of different drugs. A recently published clinical trial randomized hypertensive patients to groups guided by the goal of PWV or peripheral BP reduction but used different classes and drugs in the follow-up phase (26).

PWV is considered an independent biomarker of subclinical TOD (27). To date, only the SPARTE study evaluated the strategy of AH treatment guided by PWV reduction compared with the strategy guided by peripheral BP and no significant differences were found to significantly CV outcomes, peripheral arterial disease, hospitalization for heart failure, aortic dissection, chronic kidney disease, and sudden death. However, the PWV guided treatment intensified the antihypertensive treatment with vascular aging prevention characterized by PWV behavior compared to the conventional treatment (26).

In our study treatment was guided with central or peripheral BP to achieve goals and considered PWV as an outcome variable. Although we found no significant difference between groups, the CG showed a significant reduction in changed PWV (≥10 m/s) over the 12-month follow-up. This finding corroborates the results of the SPARTE study and others that evaluated strategies to reduce vascular aging velocity (26–28).

In addition to PWV, our study also analyzed AIx, central BP, TVR, and central pulse pressure (CPP). We found a difference in central diastolic BP after a 12-month follow-up between the two randomized groups. Several studies evaluated these biomarkers, mainly as attempted surrogate outcome, and observed no significant association between central and peripheral BP measurements (29–32). However, a systematic review showed greater predictive power of central BP and CPP for TOD and CV outcomes (32). AIx was higher in the CG and reversed this behavior after the one-year follow-up.

Currently, evidence shows a stronger association between the central component of BP and increased LVMI and carotid IMT (33). Increased arterial stiffness is believed to be an intermediate stage between aging and CV damages, such as left ventricular and carotid dysfunction (34, 35). Our study showed no benefit in reducing CV outcomes such as left ventricular hypertrophy (LVH) and carotid vascular damage when treating hypertensive patients based on central BP compared with peripheral BP, and the frequency of subjects with changed LVMI reduced in both groups at the end of follow-up.

Two other studies that used the electrocardiogram as a measure of LVH showed a good association between central BP and LVH, but similar to that observed between peripheral systolic BP and LVH (36, 37). Another study reported the better predictive value of central BP compared to peripheral BP for cardiac damage such as LVH (38). A possible explanation is that arterial stiffness increases systolic BP, causing an early return of pulse waves during the systolic period and increased left ventricle afterload that causes cardiac hypertrophy and consequent LVH (39–41).

In our study, central BP had no better association with renal impairment than peripheral BP, a finding that corroborates with those of previous outpatient studies (42, 43). This may be justified by the fact that central BP is associated with macrovascular

damage, but is not so closely related to microvascular injury, typical of renal injury (9). Another hypothesis suggests that in the early stages of kidney disease, the association between BP and kidney damage may be weak (44). We believe that longer follow-up and/or a larger sample size may detect greater CV protection with targets guided by central BP reduction.

The limitations of our study were mainly related to the loss of follow-up due to the COVID-19 pandemic, which may have impacted the statistical power to demonstrate differences between groups. Another limitation is related to a sample with well-controlled BP levels at the beginning of the study, which hinders differences in outcomes closely related to BP control. However, this is an unprecedented clinical trial in the comparison of goals guided by different strategies and with results that raise the need for further studies to provide the desired answers.

This clinical trial tested a hypothesis that is still under construction. Nevertheless, the intergroup difference in the behavior of AIx, central diastolic BP, and intragroup difference regarding the frequency of changed PWV and LVMI makes it plausible to consider the benefits of the treatment guided by central parameters.

Conclusion

The treatment of hypertensive disease guided by central pressure reduction goals was not able to demonstrate differences in outcomes related to PWV, LVMI, IMT, and renal function compared to the traditional strategy, but showed superiority in reducing central diastolic pressure and AIx behavior at the end of a one-year follow-up. Intragroup analysis found a lower frequency of PWV $\geq$10 m/s in the CG, raising the hypothesis that longer follow-ups and greater sampling power may demonstrate the benefits of this treatment strategy.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comitê de ética em pesquisa do Hospital das Clínicas da Universidade Federal de Goiás, Brasil. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

WB: Conceived and designed the analysis; Collected the data; Contributed data or analysis tools; Performed the analysis; Wrote the paper. GG: Collected the data; Contributed data or analysis tools; Wrote the paper. PO: Conceived and designed the analysis; Collected the data; Contributed data or analysis tools; Performed the analysis; Wrote the paper. SI: Collected the data; Contributed data or analysis tools; Performed the analysis; Wrote the paper. AB: Collected the data; Contributed data or analysis tools. RP: Collected the data; Contributed data or analysis tools. VM: Collected the data; Contributed data or analysis tools. LO: Collected the data; Contributed data or analysis tools. AS: Conceived and designed the analysis; Collected the data; Contributed data or analysis tools; Performed the analysis. AC: Conceived and designed the analysis; Contributed data or analysis tools; Wrote the paper. PV: Conceived and designed the analysis; Contributed data or analysis tools; Wrote the paper. All author contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Hypertension evaluated in the public and private Brazilian health system hypertension in public and private service

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Introduction: Hypertension (HT) remains the leading cause of death worldwide. In Brazil it is estimated that 35% of the adult population has HT and that about 20% of these have blood pressure values within the targets recommended for the reduction of cardiovascular risk. There are some data that point to different control rates in patients treated by cardiologists in public and private referral center and this is an important point to be investigated and discussed.
Objective: To compare sociodemographic characteristics, body mass index (BMI), antihypertensive (AH) drugs, blood pressure (BP) and control rate in public (PURC) and private (PRRC) referral centers.
Methodology: A cross-sectional multicenter study that analyzed data from hypertensive patients assisted by the PURC (one in Midwest Region and other in Northeast region) and PRRC (same distribution). Variables analyzed: sex, age, BMI, classes, number of AH used and mean values of systolic and diastolic BP by office measurement and home blood pressure measurement (HBPM). Uncontrolled hypertension (HT) phenotypes and BP control rates were assessed. Descriptive statistics and χ^2 tests or unpaired t-tests were performed. A significance level of $p < 0.05$ was considered.
Results: A predominantly female (58.9%) sample of 2.956 patients and a higher prevalence of obesity in PURC ($p < 0.001$) and overweight in PRRC ($p < 0.001$). The mean AH used was 2.9 ± 1.5 for PURC and 1.4 ± 0.7 for PRRC ($p < 0.001$). Mean systolic and diastolic BP values were higher in PURC as were rates of uncontrolled HT of 67.8% and 47.6% ($p < 0.001$) by office measurement and 60.4% and 35.3% ($p < 0.001$) by HBPM in PURC and PRRC, respectively.
Conclusion: Patients with HT had a higher prevalence of obesity in the PURC and used almost twice as many AH drugs. BP control rates are worse in the PURC, on average 15.3 mmHg and 12.1 mmHg higher than in the PRRC by office measurement.

KEYWORDS

hypertension, public health system, private health system, targets, treatment

Introduction

Hypertension (HT) remains the leading cause of death worldwide. Despite this, it remains underdiagnosed and undertreated (1). In Brazil, it is estimated that 35% of the adult population has HT and that about 20% of these have blood pressure (BP) values within the targets recommended for the reduction of cardiovascular (CV) risk (2).

However, when we evaluate the rates of HT control in patients treated by cardiologists and in private services, the values found are better than those described in the databases of patients assisted in the Unified Health System (SUS) and can reach 60.6% (3–6).

Further, it is well established that both diagnosis and assessment of HT control by BP monitoring methods are more accurate than office measurement and should be performed whenever possible (2, 7, 8).

Given this scenario this study aimed to compare BP values and BP control among hypertensive patients followed up in public referral center (PURC) and private referral centers (PRRC), located in two regions of Brazil (Midwest and Northest) under the coordination of the same medical team and following the same treatment protocols established by the Brazilian Guidelines on Hypertension (2).

Methods

Study design and participants

A cross-sectional multicenter study that analyzed data from patients with HT assisted by the PURC and PRRC obtained from an online platform (*telemrpa.com.br*) between the years 2017 and 2021. The BP values were recorded and stored in the equipment memory and were then included in the TeleMRPA® platform, a telemedicine tool for providing remote reports.

Participants needed to be 18 years of age with a diagnosis of HT and in the use of antihypertensive (AH) drugs to be included. All patients with these criteria were included. The sample was calculated considering a prevalence of HT in Brazil of 32.3% (2). A minimum sample of 583 participants was obtained. This study was submitted to and approved by the Ethics Committee on Human Research of the Hospital das Clínicas of the Universidade Federal de Goiás (registration number: CAAE 99691018.7.0000.5078), which waived the need for an informed consent form.

Variables

Baseline clinical variables were collected at the time of home blood pressure measurement (HBPM) and comprised the following data: age, sex, body mass index (BMI) using Quetelet's formula (9), classes and number of AH used, mean values of systolic blood pressure (SBP) and diastolic blood pressure (DBP) by office measurement and by HBPM.

Nutritional status was classified as overweight (yes or no), obesity (yes or no). and overweight (yes or no). Overweight was considered as those classified as overweight and obese I, II or III (9).

OMRON brand automatic digital devices were used for BP measurements. The HT was standardized through the protocols of the Brazilian Guidelines for Ambulatory Blood Pressure Monitoring and Guidelines for Residential Monitoring of Blood Pressure 2018 (7). Six measurements were performed per day, three in both the morning (upon waking) and evening/night (before dinner or two hours after), respectively, with one-minute intervals for a total of 24 valid measurements being standardized to at least 14 as an acceptable quality standard. Discrepant measurements such as SBP > 250 mmHg or <70 mmHg; DBP > 140 mmHg or <40 mmHg and pulse pressure (PP) >100 mmHg or <20 mmHg were excluded. Controlled HT was defined as SBP < 140 mmHg and DBP < 90 mmHg considering office measurement or SBP < 130 mmHg and DBP < 80 mmHg by HBPM (2).

Statistical analysis

Continuous variables with normal distribution were presented as mean and standard deviation while those without normal distribution were presented as median (25th, 75th percentiles). Categorical variables were presented as proportions.

To compare the variables between the groups studied the following statistical tests were used: *Student'st*-test for continuous variables with normal distribution, *Mann-Whitney test* for continuous variables without normal distribution and χ^2 for categorical variables. A-value of $p < 0.05$ was considered statistically significant. Analyses were performed using STATA version 14 *software*.

Results

A total of 2.956 participants were evaluated, of which 1.789 (60.5%) and 1.167 (39.5%) were from the PRRC and PURC groups respectively with no age difference. The frequency of males was higher in the private service (**Table 1**).

As for nutritional status, only 21.7% of the sample was not overweight with a higher prevalence of obesity in the PURC compared to the PRRC.

Regarding antihypertensive drugs, the use of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) was similar in both groups. However, all other classes have a higher frequency of use in patients followed up in the public service. The mean number of antihypertensives used was 2.0 ± 1.3 for the total sample; 1.4 ± 0.7 for PRRC and 2.9 ± 1.5 for PURC ($p < 0.001$) (**Table 1**).

All mean blood pressure values, both from office measurements and HBPM in the PURC and PRRC are described in **Table 2**. The frequency of uncontrolled HT was higher in the PURC both by office measurements and by HBPM (**Figure 1**).

TABLE 1 Comparison of sociodemographic characteristics between private and public referral centers.

	Total ($n = 2,956$)	Private ($n = 1,789$)	Public ($n = 1,167$)	
Sex ($n = 2,955$)				<0.001
Female	1.742 (58.9)	975 (54.5)	767 (65.7)	
Male	1.213 (41.1)	813 (45.5)	400 (34.3)	
Age (years)	58.8 ± 12.2	58.6 ± 12. 8	59.3 ± 11.3	0.183
Age Group				0.080
18–59 years old	1.419 (48.0)	882 (49.3)	537 (46.0)	
60 years or older	1.537 (52.0)	907 (50.7)	630 (54.0)	
Obesity				<0.001
No	1.826 (62.6)	1.172 (65.5)	654 (58.0)	
Yes	1.090 (37.4)	617 (34.4)	473 (42.0)	
Overweight				<0.208
No	633 (21.7)	402 (22.5)	231 (20.5)	
Yes	2.283 (78.3)	1.837 (77.5)	896 (79.5)	
Nutritional status				<0.001
Normal weight	633 (21.7)	492 (22.4)	231 (20.5)	
Overweight	1.193 (40.9)	770 (43.0)	423 (37.5)	
Obesity	1.090 (37.4)	617 (34.5)	473 (42.0)	
Number of medications				
BRA	1.762 (59.6)	1.063 (59.4)	699 (59.9)	0.796
IECA	840 (28.4)	502 (28.0)	338 (28.9)	0.595
Thiazide Diuretic	1.048 (35.4)	398 (22.5)	650 (55.7)	<0.001
BCC	1.212 (41.0)	654 (36.7)	558 (47.8)	<0.001
Beta-blocker	960 (32.5)	381 (21.3)	579 (49.6)	<0.001
Potassium saver	268 (9.1)	60 (3.3)	208 (17.8)	<0.001
Alpha 2 agonists	206 (7.0)	31 (1.7)	175 (15.0)	<0.001
Vasodilators	93 (3.1)	4 (0.2)	89 (7.6)	<0.001
Loop Diuretic	107 (3.6)	9 (0.5)	98 (8.4)	<0.001

X^2, ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker.

TABLE 2 Comparison of body mass index and pressure values between private and public referral centers.

	Total	Private	Public	*p*
BMI (Kg/m^2)	28.9 ± 5.2	28.6 ± 4.8	29.4 ± 5.7	**<0.001**
Office pressure				
SBP (mmHg)	135.9 ± 21.9	130.6 ± 17.2	144.0 ± 25.5	**<0.001**
DBP (mmHg)	84.0 ± 12.3	81.9 ± 10.2	87.3 ± 14.4	**<0.001**
HBPM				
SBP (mmHg)	127.7 ± 17.6	123.6 ± 13.6	134.0 ± 20.8	**<0.001**
DBP (mmHg)	78.9 ± 11.0	76.9 ± 8.9	82.0 ± 13.0	**<0.001**
PP (mmHg)	53.3 ± 14.4	51.0 ± 12.6	56.6 ± 16.2	**<0.001**
Max morning SBP (mmHg)	128.2 ± 18.0	123.9 ± 14.1	134.7 ± 21.2	**<0.001**
Max morning DBP (mmHg)	80.0 ± 11.4	77.9 ± 9.5	83.1 ± 13.3	**<0.001**
SBP variability morning	8.18 ± 3.6	7.5 ± 3.2	9.2 ± 3.9	**<0.001**
PAD variability morning	4.8 ± 2.5	4.6 ± 2.3	5.4 ± 2.6	**<0.001**

Unpaired *t*-test. BMI, body mass index; HBPM, residential blood pressure monitoring; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure. Bold values are statistically significant.

Regarding the possible phenotypes of uncontrolled BP in treated patients with HT, the frequency of sustained hypertension (SH), when both office BP and HBPM are above the recommended targets, was higher in the SRPU. However, masked hypertension (MH) was more frequent in PRRC (**Figure 2**).

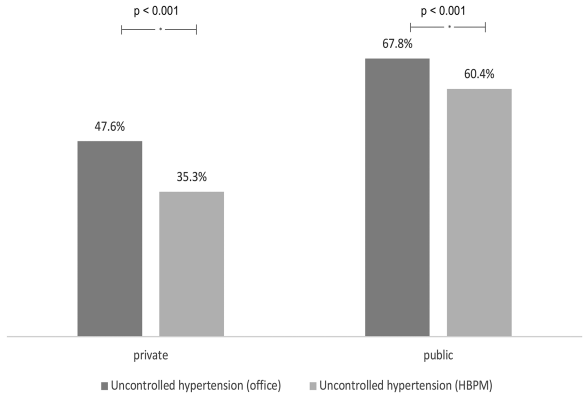

FIGURE 1
Comparison of the frequency of uncontrolled hypertension between public and private services considering office measures and home blood pressure measurement (HBPM).

Furthermore, we evaluated all 904 patients (30.6%) who were using 3 or more classes of antihypertensive drugs in combination. Further, we found this subgroup had a higher prevalence of uncontrolled HT in the PURC (**Figure 3**).

Discussion

The sample evaluated consisted of people with HT with an average age of just under 60 years and an overweight average body mass index. We observed a higher prevalence of females in the total sample, with an even higher prevalence in the PURC. This characteristic of higher frequency of medical care by females has already been described in other publications and denotes the lack of attention to men's health concerning HT (10, 11).

Another important aspect observed in the sample was the higher overweight prevalence in the PRRC (43.0%) and obesity in the PURC (42%). Such characteristics may denote a poorer quality diet and an increased association with comorbidities or severity of hypertensive disease in patients in the public service because it is known that increased BMI and abdominal circumference are risk factors for both increased BP and major cardiovascular diseases (12–14). Moreover, socioeconomic and cultural barriers, in general, are associated with the differences in BMI found both in our sample and in other analyses already published (15, 16).

PURC patients used a greater number of antihypertensive medications. Moreover, except for the classes that block the renin-angiotensin-aldosterone system (ACEI or ARB), the other classes were used more frequently in the PURC. As for antihypertensives available for use in the basic health network in our country, most of them have short half-lives and we do not have fixed combinations in a single pill. This reality leads to the need for the use of a greater number of drugs, pills and daily doses. This is known to be associated with lower adherence to treatment and resulting worsening in BP control (2, 5, 17, 18). We should also consider that there was a higher prevalence of obesity in the PURC, a factor associated with pressure levels that are more difficult to control (2, 5, 17, 18).

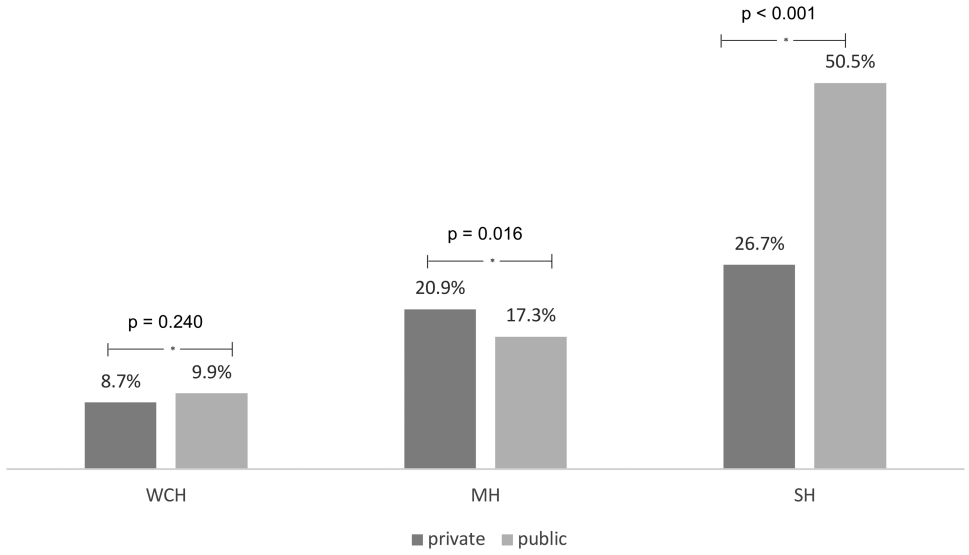

FIGURE 2
Comparison of the frequency of hypertension phenotypes between public and private services considering office measures and that of residential blood pressure monitoring. WCH, whit-coat hypertension; MH, masked hypertension; SH, sustained hypertension.

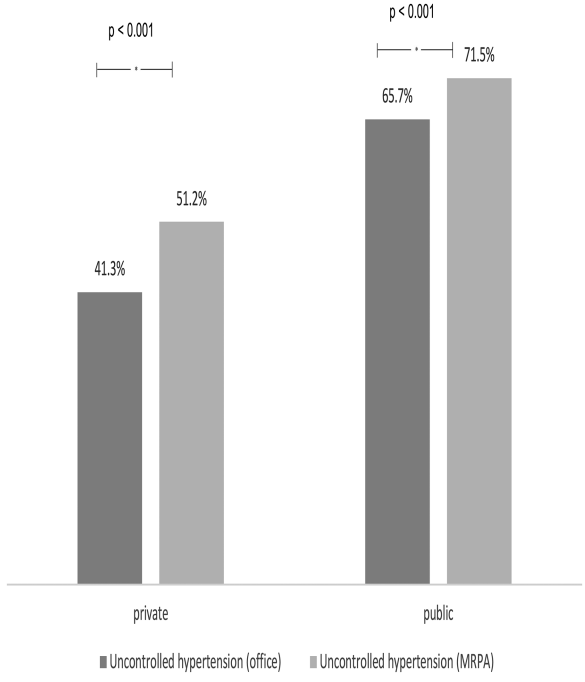

FIGURE 3
Comparison of the frequency of uncontrolled hypertension in patients using more than three medications between public and private services considering office measurements and HBPM.

Despite the greater number of AH used in PURC, the mean SBP and DBP values, whether measured in the office or by HBPM remained significantly higher than in PRRC. The consequence of a higher number of uncontrolled patients is an increase in the incidence of major associated CV outcomes. Effectively improving the control of HT means dramatically reducing the incidence of stroke, acute myocardial infarction, heart failure and chronic kidney disease (19–21).

When we evaluated the possible phenotypes of uncontrolled HT, we found a higher prevalence of SH in the PURC. This phenotype is the one with the worst prognosis relating to cardiovascular outcomes in hypertensive patients since it denotes a lack of BP control in both office measurements and HBPM (22). This aspect reinforces the importance of assessment, whenever possible, through BP monitoring methods. This way, we will have a broader understanding of the BP control status and the best strategies for pharmacological treatment (23). In a previous study of patients with HT treated by specialist physicians and evaluated by HBPM, SH rates were 33.7% (6); in our sample we found values of 50.7% and 26.7% in PURC and PRRC, respectively ($p < 0.001$).

When evaluating the subgroup using three or more AH drugs, we found higher levels of patients off target by both the office measure and HBPM which was to be expected and similar to the total sample, those followed up in the PURC had worse control rates than the PRRC group.

This study has some limitations since we have not evaluated socio economic level and adhesion with specific tools, however, by evaluating a population of more than 3,000 hypertensive patients using public and private reference centers under the same coordination, we believe it is possible to evaluate with less bias the aspects related to drug use in both scenarios and the impact on BP control. Furthermore, the information obtained both by the office measurement and by the HBPM allows greater accuracy in the evaluation of the recommended goals.

It was possible to observe that patients followed up in public referral centers have a higher prevalence of obesity and use more than double the number of antihypertensive drugs than private services.

The blood pressure control rates assessed by both office measurement and HBPM are always worse in the PURC and on

average 15.3 mmHg and 12.1 mmHg higher than in the PRRC for SBP and DBP, respectively, in the office measurements.

The poorer control of HT is associated with a higher incidence of the main cardiovascular outcomes. Therefore, there is an urgent need to reassess strategies so that, in the end, we can decrease the disparities between public and private services and increase our hypertensive population's cardiovascular protection.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comitê de Ética em Pesquisa do Hospital das Clínicas, Universidade Federal de Goiás, Brasil. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because the data do not identify participants and are retrospective.

Author contributions

KA: Investigation, Methodology, Writing – original draft, Writing – review & editing. PV: Conceptualization, Data curation, Formal Analysis, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. AF: Data curation, Methodology, Supervision, Validation, Visualization, Writing – review & editing. MS: Formal Analysis, Methodology, Supervision, Visualization, Writing – review & editing. RB: Formal Analysis, Supervision, Validation, Visualization, Writing – review & editing. LL: Investigation, Methodology, Writing – original draft, Writing – review & editing. MC: Conceptualization, Data curation, Formal Analysis, Supervision, Visualization, Writing – review & editing. AC: Conceptualization, Formal Analysis, Supervision, Validation, Writing – review & editing. AS: Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. WB: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Waist circumference cut-off points to identify major cardiovascular events and incident diabetes in Latin America: findings from the prospective Urban rural epidemiology study Colombia

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Background: Abdominal obesity (AO) indirectly represents visceral adiposity and can be assessed by waist circumference (WC) measurement. In Latin America, cut-off points for the diagnosis of AO are based on Asian population data. We aim to establish the WC cut-off points to predict major cardiovascular events (MACE) and incident diabetes.

Methods: We analyzed data from the cohort PURE study in Colombia. WC cut-off points were defined according to the maximum Youden index. Multivariate logistic regression was used to obtain associations between WC and MACE, diabetes, and cumulative incidence of outcomes visualized using Kaplan-Meier curves.

Results: After a mean follow-up of 12 years, 6,580 individuals with a mean age of 50.7 ± 9.7 years were included; 64.2% were women, and 53.5% were from rural areas. The mean WC was 85.2 ± 11.6 cm and 88.3 ± 11.1 cm in women and men, respectively. There were 635 cases of the MACE composite plus incident diabetes (5.25 events per 1,000 person-years). Using a cut-off value of 88.85 cm in men (sensitivity = 0.565) and 85.65 cm in women (sensitivity = 0.558) resulted in the highest value for the prediction of the main outcome. These values were associated with a 1.76 and 1.41-fold increased risk of presenting the composite outcome in men and women, respectively.

Conclusions: We defined WC cut-off points of 89 cm in men and 86 cm in women to identify the elevated risk of MACE and incident diabetes. Therefore, we suggest using these values in cardiovascular risk assessment in Latin America.

KEYWORDS

abdominal obesity, waist circumference, major cardiovascular events, diabetes, Latin America

Abbreviations

WC, waist circumference; MACE, major adverse cardiovascular events; IDF, international diabetes federation; BMI, body mass index; CVD, cardiovascular disease; ANOVA, analysis of variance; HR, hazard ratio; ROC, receiver operating characteristic curve; AO, abdominal obesity; PURE, prospective Urban rural epidemiology.

1. Introduction

Cardiovascular disease (CVD) remains the principal cause of morbidity and mortality in Latin America and worldwide (1, 2). It has been demonstrated that modifiable risk factors explain approximately 70% of major cardiovascular events (MACE) (2–4). Among these risk factors, abdominal obesity (AO) contributes to 15% of the population attributable fraction, a higher percentage than other risk factors such as smoking or dyslipidemia (1). AO indirectly represents visceral adipose tissue accumulation and can be quantified by various methods, most commonly the simple and easily applicable waist circumference (WC) measurement using a tape measure. WC measuring is usually taken at the midpoint between the inferior costal margin and the iliac crest. Large-scale observational data shows that as WC increases, the number of cardiovascular risk factors, cardiovascular mortality, and all-cause mortality increases (5–8). In addition, from a metabolic perspective, crosstalk of inflammatory signals between visceral adiposity and insulin-dependent cells leads to an increased risk of developing diabetes (9). Several studies in different geographical populations and ethnicities have confirmed the association between AO and diabetes (10, 11).

A high WC is also a cornerstone component of the metabolic syndrome diagnosis. The International Diabetes Federation (IDF) determined that the WC cut-off points used for AO should be specific to geographic location (12), with distinct values for Europe, the United States, and Southeast Asia. With respect to Latin America, including Central and South America, IDF recommends that until more information is available, cut-off points for Asian countries (≥80 cm in women and ≥90 cm in men) be used. This recommendation was made more than 15 years ago and is still applied in the clinical setting, but it has also led to multiple studies in Latin America aimed at clarifying associations in this population. Most of these studies were cross-sectional and showed that specific WC cut-off points are associated with the intra-abdominal fat volume measured by computed tomography or with metabolic and inflammatory alterations (13–18). However, these measured outcomes have generated debate about their applicability in clinical prognosis. In Latin America, there also remains a paucity of follow-up cohort/prospective data upon which to define region-specific WC cut-off points that predict MACE and diabetes. Therefore, this study aims to establish the WC cut-off points with the greatest capacity to predict MACE and incident diabetes in the Colombian population of the Prospective Urban Rural Epidemiology (PURE) study.

2. Materials and methods

2.1. Study design, population, sociodemographic and clinical data

The PURE study is a large-scale prospective multinational cohort study including high, middle, and low-income countries. The study design, including sample size, has previously been reported (19). For the present analysis, we included 6,580 with complete data. A multistage convenience sample survey was used, and a representative sample of households was recruited using a community-sampling framework. Households were eligible if at least one member was 35–70 years old and if the members intended to continue living at that address for 4 years or more. The participants were selected from urban and rural communities in 11 departments of the country. After informed consent was obtained, questionnaires were applied to identify sociodemographic, clinical, and anthropometric data. Demographic characteristics such as area of residence and socioeconomic characteristics such as educational level was recorded. In addition, the history of cardiometabolic events and associated risk factors were examined. Current smokers were defined as those who reported having used a tobacco product in the past 12 months. Current alcohol consumption was defined as those who declared alcohol consumption in the last year. Every year, the participants are followed up by telephone to inquire about their vital status and the outcomes. Every three years, in addition to the telephone contact, a broader questionnaire is made inquiring about lifestyles and access to health services. In addition, anthropometric and laboratory measurements are made according to the protocol. For the analysis, we used the baseline measurements (between 2005 and 2009) and presential follow-up visits (mean follow-up of 12 ± 2.3 years) to identify cardiometabolic outcomes.

2.2. Anthropometric measures

Anthropometric measurements were acquired following the PURE standardized protocol. Body weight was obtained using a digital scale, ensuring that the patient wore light clothing, and height was obtained using a tape measure, approximating each measurement to the nearest centimeter. The patient was instructed to be barefoot for both measurements. WC and hip circumference were measured with tape on the patient's skin. WC was considered the smallest circumference between the lower costal margin and the upper margin of the iliac crest. The hip circumference was measured at the level of the greater trochanters. Body mass index (BMI) by dividing body weight (in kilograms) by height (in meters) squared.

2.3. Outcomes

The main MACE composite outcome was defined as the occurrence of cardiovascular death, myocardial infarction, stroke, or heart failure, whichever came first. Myocardial infarction was defined as typical or symptoms suggestive of a heart attack according to the medical professional associated with electrocardiogram changes or changes in biomarkers; stroke as an acute focal neurological deficit diagnosed by a physician and thought to be of vascular origin (without another case such as a brain tumor) with signs and symptoms lasting ≥24 h; finally,

heart failure was defined as signs (rales, increased jugular venous pressure, or ankle edema) or symptoms (paroxysmal nocturnal dyspnea, dyspnea at rest, or ankle edema) of congestive heart failure and one or both of the following: radiological studies of pulmonary congestion, treatment of heart failure with diuretics. Diabetes was defined as fasting blood glucose >126 mg/dl or a history of diabetes (self-reported) or current diabetes treatment. The outcome variables were taken with a cut-off date of February 28, 2021.

2.4. Statistical analysis

Continuous variables were presented as means and standard deviations. Categorical variables were presented as absolute frequencies and percentages. The analysis of variance (ANOVA) method was used to examine differences between continuous variables and Pearson's chi-square test between categorical variables. First, WC cut-off points for maximum sensitivity and specificity for the presence or absence of the time to event outcomes (MACE, fatal and non-fatal stroke, fatal and non-fatal myocardial infarction, fatal MACE, diabetes and the MACE and diabetes composite) were determined with the maximum Youden index. The ROC curves and the integrated area under the curve iAUC (20) were estimated for censored survival data at 12 years of follow-up using the risksetROC library version 1.0.4.1. Second, Kaplan-Meier curves were used to visualize the cumulative incidence of the composite outcome splitting by the previously established cut-off points. Third, the association between the WC cut-off points and the composite outcome was analyzed using the Cox proportional hazards model with random effects given by the Colombian provinces estimating hazard ratio (HR) and 95% confidence intervals (CI), using the coxme version 2.2–18.1. All statistical analyses were conducted using the R software version 4.2.2. All p values were two-sided, and the significance level was 5%.

3. Results

At the baseline, the overall mean age was 50.7 ± 9.7 years, 4,845 (64.2%) participants were women, and 53.5% of the population were from rural areas. In addition, women had a WC mean of 85.2 ± 11.6 cm, while men had 88.3 ± 11.1 cm. Other baseline characteristics are shown in **Table 1**. During a median follow-up of 12 ± 2.3 years, there were 419 events of the MACE composite, 138 cardiovascular deaths, 184 incident cases of myocardial infarction, 88 incident cases of stroke, 304 cases of incident diabetes, and 635 cases of the MACE composite plus incident diabetes (5.25 events per 1,000 person-years). The assessment for the optimal performance of WC cut-off points according to sex to identify individuals at risk of composite MACE and incident diabetes is shown in **Table 2**.

TABLE 1 Baseline characteristics of study participants.

Characteristics	Total	Female	Male	p value
Participants, n (%)	7,552	4,845 (64.2)	2,707 (35.8)	
Ages, years, mean (SD)	50.78 (9.74)	50.57 (9.60)	51.15 (9.96)	0.018
Location				
Rural, n (%)	4,043 (53.5)	2,378 (49.1)	1,665 (61.5)	<0.001
Urban, n (%)	3,509 (46.5)	2,467 (50.9)	1,042 (38.5)	
Education level				
Low, n (%)	4,988 (66.2)	3,142 (65.0)	1,846 (68.2)	0.003
Middle, n (%)	1,480 (19.6)	1,004 (20.8)	476 (17.6)	
High, n (%)	1,072 (14.2)	688 (14.2)	384 (14.2)	
Cigarette smoking				
Ex -smoker, n (%)	1,561 (20.7)	705 (14.6)	856 (31.7)	<0.001
Current, n (%)	1,045 (13.9)	446 (9.2)	599 (22.2)	
Never, n (%)	4,931 (65.4)	3,685 (76.2)	1,246 (46.1)	
Consumption of alcohol				
Ex -drinker, n (%)	1,184 (15.7)	568 (11.7)	616 (22.8)	<0.001
Current, n (%)	2,128 (28.2)	784 (16.2)	1,344 (49.6)	
Never, n (%)	4,235 (56.1)	3,488 (72.1)	747 (27.6)	
Hypertension, n (%)	2,846 (37.7)	1,869 (38.6)	977 (36.1)	0.037
Diabetes, n (%)	424 (5.6)	286 (5.9)	138 (5.1)	0.162
Ischemic cardiopathy, n (%)	183 (2.4)	118 (2.4)	65 (2.4)	0.985
Heart failure n (%)	115 (1.5)	78 (1.6)	37 (1.4)	0.466
Stroke n (%)	113 (1.5)	82 (1.7)	31 (1.1)	0.076
Other cardiovascular diseases, n (%)	105 (1.4)	77 (1.6)	28 (1.0)	0.061
Waist circumference, mean (SD)	86.3 (11.5)	85.2 (11.6)	88.3 (11.1)	<0.001
Hip circumference, mean (SD)	97.6 (10.1)	99.3 (10.2)	94.7 (9.2)	<0.001
Body mass index, mean (SD)	26.2 (4.6)	26.8 (4.9)	25.2 (4.1)	<0.001

SD, standard derivation; p value: analysis of variance (ANOVA) of one factor (continuous variables), and Pearson's chi-square test (categorical variables).

TABLE 2 Optimal cut-off points for waist circumference to identify Major cardiovascular events and incident diabetes. *n* = 6,580.

	Proposed cutt-off point (cm)	AUC	Sensitivity	Specificity	Youden index	Sensitivity with IDF cut-off point[b]	Specificity with IDF cut-off point[b]	Youden index
Male								
MACE[a]	88.2	0.571	0.526	0.574	0.100	0.455	0.643	0.098
Incident diabetes	90.9	0.699	0.619	0.666	0.285	0.650	0.634	0.284
MACE + diabetes	88.85	0.613	0.565	0.595	0.159	0.517	0.641	0.158
Female								
MACE[a]	85.55	0.596	0.545	0.591	0.136	0.729	0.391	0.121
Incident diabetes	86.65	0.646	0.578	0.629	0.207	0.777	0.393	0.176
MACE + diabetes	85.65	0.613	0.558	0.602	0.160	0.737	0.404	0.141

MACE, Mayor adverse cardiovascular events; AUC, area under the curve; Youden index, sensitivity + 1−specificity.
[a]MACE: composite of cardiovascular death, myocardial infarction, heart failure, and stroke.
[b]IDF cut-off point: 90 cm in men and 80 cm in women.

With a cut-off value of 88.85 cm in men (sensitivity = 0.565), and 85.65 cm in women (sensitivity = 0.558) the Youden index was the highest for the identification of the composite of MACE plus incident diabetes (1,233 in men and 1,203 in women). The ROC curve for the main outcome is shown in **Figure 1**. The AUC was 0.613 in men and 0.613 in women. In addition, the optimal WC cut-off points were positively associated with the risk of presenting the outcome composite (**Table 3**). After establishing a WC cut-off value of 89 cm, men above this value had a 1.76-fold increased risk of presenting the composite outcome (HR = 1.76, 95% CI: 1.26–2.45). A WC cut-off value greater or equal to 86 cm in women had a 1.41-fold higher risk (HR = 1.46, 95% CI: 1.09–1.83) (**Figure 2**).

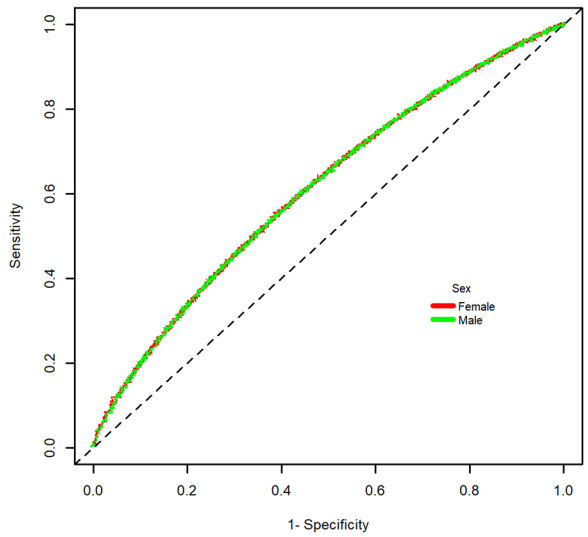

FIGURE 1
ROC curve for major cardiovascular events or incident diabetes from waist circumference.

4. Discussion

4.1. Key findings

In this analysis of a prospective cohort study with more than 6,500 Colombian adults and a mean follow-up of 12 years, we demonstrated that the optimal WC cut-off point to identify the risk of the composite of MACE and incident diabetes is 89 cm in men and 86 cm in women. Since 2006, when the IDF metabolic syndrome guidelines recommended taking WC cut-off points for determining AO derived from the population of Southeast Asia in the absence of data in Latin America, multiple studies have been carried out to identify the optimal value for our population.

The Peruvian Study of Cardiovascular Disease (PREVENCION) (13) in 1,439 adults showed that cut-off points of 97 cm in men and 87 cm in women were associated with subclinical atherosclerotic disease (defined by the thickness of carotid intima-media) or overt CVD including diabetes as an equivalent of vascular disease risk. The values in the present study resemble those found primarily in women; however, PREVENCION was a cross-sectional study in an Andean population of southern Peru at 2,335 meters above sea level, making it difficult to generalize the results. In contrast, the PURE Colombia study was carried out in 11 departments with different altitudes and representativeness of roughly 51% of the Colombian population from different ethnic groups. The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) also evaluated the cut-off points of WC in other Latin American populations. Their results align with ours, especially in women, where the optimal cut-off points were the same (86 cm). Unlike our study, in the ELSA-Brasil study, the outcomes assessed were intermediate (metabolic parameters), contrary to MACE and diabetes evaluated in the present study. In addition, the study mentioned above had a cross-sectional nature. In contrast, the data from PURE-Colombia have a prospective average follow-up of 12 years, enabling the evaluation of "hard" outcomes (21).

Recently, the cross-sectional Hispanic Community Health Study/Study of Latinos (HCHS/SOL) evaluated 16,415 self-identified Hispanic/Latino subjects residing in the United States (14). The results suggested an optimal cut-off point of 102 cm and 97 cm in men and women, respectively, to discriminate the risk of ischemic heart disease. Men's cut-off points are like those

TABLE 3 Association between optimal waist circumference cutoff point with Major cardiovascular events and diabetes.

	Male				Female			
	Univariate		Multivariate[a]		Univariate		Multivariate[a]	
	HR (CI95%)	*p* value	HR (CI95%)	*p* value	HR (CI95%)	*p* value	HR (CI95%)	*p* value
MACE[b]	1.77 (1.29–2.42)	<0.001	1.55 (1.04–2.30)	0.031	1.91 (1.47–2.47)	<0.001	1.24 (0.89–1.72)	0.200
Cardiovascular mortality	1.35 (0.83–2.17)	0.220	1.10 (0.59–2.05)	0.760	2.82 (1.71–4.67)	<0.001	1.73 (0.94–3.21)	0.080
Myocardial infarction	1.73 (1.11–2.69)	0.015	1.54 (0.88–2.70)	0.130	2.60 (1.70–3.97)	<0.001	1.60 (0.95–2.71)	0.080
Stroke	1.77 (0.92–3.44)	0.089	1.33 (0.57–3.11)	0.500	1.61 (0.92–2.81)	0.092	1.26 (0.62–2.55)	0.530
Incident diabetes	5.54 (3.39–9.06)	<0.001	3.58 (2.07–6.18)	<0.001	2.76 (2.07–3.66)	<0.001	1.56 (1.10–2.22	0.013
MACE + Diabetes	2.36 (1.79–3.11)	<0.001	1.76 (1.26–2.45)	0.001	2.32 (1.88–2.86)	<0.001	1.41 (1.09–1.83)	0.009

MACE, Mayor adverse cardiovascular events; IC95%, confidence interval 95%; HR, hazard ratio; *p*-value, Univariate and multivariate regression models of proportional hazards with random effects.

[a]Models were adjusted for age, location (urban/rural), level of education, tobacco and alcohol consumption, history of hypertension and body mass index.

[b]MACE, composite of cardiovascular death, myocardial infarction, heart failure, and stroke.

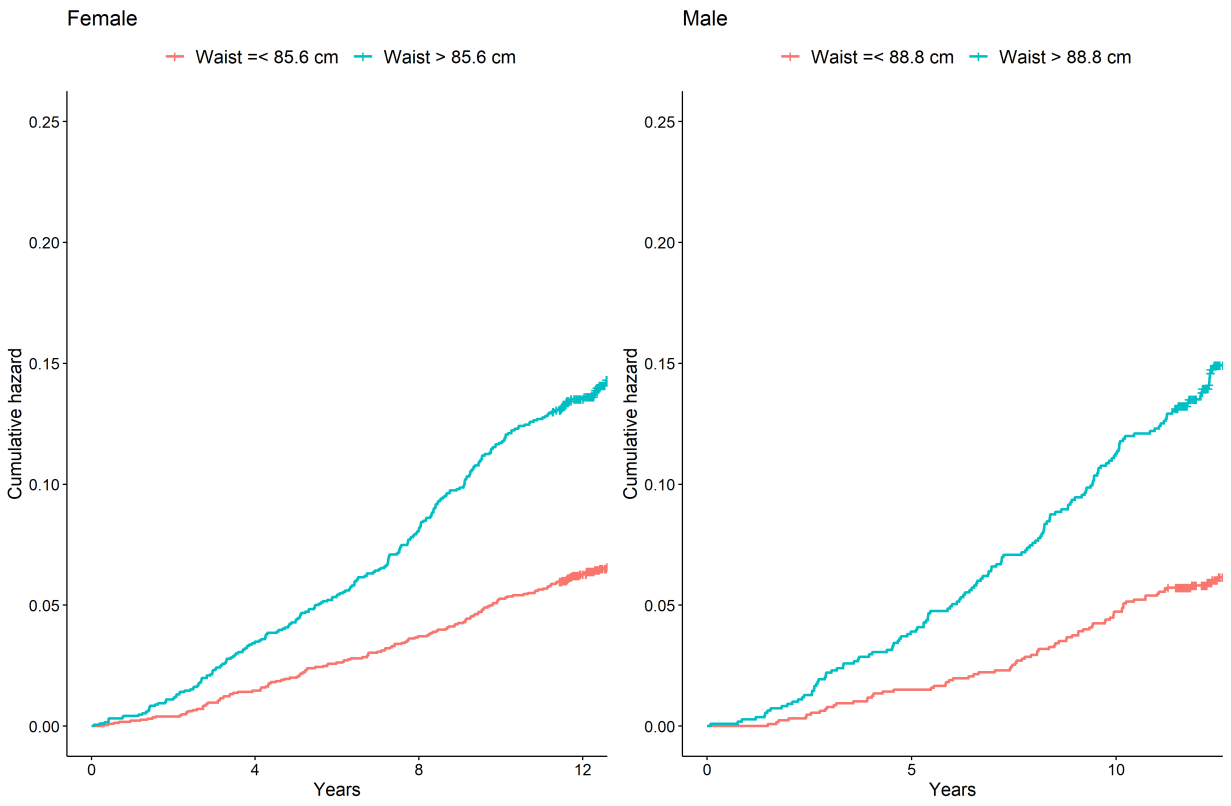

FIGURE 2
Cumulative incidence of major cardiovascular events and incident diabetes by waist circumference higher or lower that 89 cm in men and 86 cm in women. Shown are Kaplan–Meier event curves for the main composite outcome of cardiovascular death, myocardial infarction, ischemic stroke, and incident diabetes.

recommended by the IDF for the non-Hispanic population of the United States. We can therefore infer an environmental influence on the risk of metabolic and CVD; and in our socioeconomic conditions, distinct from those of high-income countries, using a higher cut-off point could lead to underdiagnosis or late identification of this cardiovascular risk factor (22).

In Colombia, in males national air force staff, a WC cut-off point of 88 cm was associated with cardiometabolic alterations, including dyslipidemia and elevation of the acute phase reactant C-reactive protein (15). Additionally, the Diagnóstico del Riesgo Cardiovascular Global study in Medellín determined practically identical values as that of our study (92 cm in men and 84 cm in women) to identify insulin resistance through the HOMA insulin resistance index (IR -HOMA) (16). The main limitation of these studies is their cross-sectional nature and intermediate outcomes. Cut-off points of 94 cm in men and 90 cm in women

have been suggested based in the area of visceral adipose tissue measured with computerized tomography scans (17). Although that area is associated with metabolic alterations that can predict cardiometabolic disease, data assessing MACE outcomes is scarce, highlighting the importance of our results. The results presented are also comparable to the recommendations made by the IDF, particularly in men. Potentially, this could be related to the sociodemographic features that influence the appearance of CVD in our population. Recent data from an analysis of the PURE study in Southeast Asia and South America showed that socioeconomic and psychosocial risk factors, such as low education, contribute a significant population-attributable risk fraction for CVD and general mortality (1, 23). In addition, the early detection of cardiovascular risk factors, in this case, a lower cut-off point in men, is of substantial importance, considering that for overall mortality, the age-standardized male-female ratio in South America is 1,72. In women, a cut-off point of 86 cm, higher than that recommended by the IDF, seems to be an appropriate value, taking into account that large observational studies such as the International Day for Evaluation of Abdominal adiposity (IDEA) showed that a cut-off point of 80 cm overestimates the definition of AO (24). The last Latin American consensus on the management of hypertension in patients with diabetes and metabolic syndrome (25) recommended carrying out a cohort study to determine the value of the abdominal perimeter best associated with hard outcomes, such as diabetes and CVD. The results of the present study that follows up this recommendation demonstrate that a WC cut-off points of 89 cm in men and 86 cm in women are the best in our population to identify the risk of diabetes and CVD.

4.2. Study limitations

However, our study has potential limitations. While the data may be representative of the Colombian population, these results may not be generalizable to the rest of Latin America. In addition, 65% of the population included were women, which limits the sample's representativeness. However, as mentioned, there is a paucity of prospective cohort studies evaluating the relationship between AO and CVD in this population. In addition, the WC measurement cannot differentiate between visceral and subcutaneous adiposity, especially in people with higher BMIs, so different imaging techniques to quantify visceral adiposity and predict cardiovascular risk should be useful. However, the measurement of WC with tape is an inexpensive, widely available tool that is applicable in clinical assessment. Although cardiovascular epidemiological studies such as INTERHEART (3) and INTERSTROKE (4) demonstrated that in the Latin American population, AO objectively measured by the waist-hip ratio is significantly associated with the appearance of the first event of myocardial infarction or stroke, the present analysis shows that a single measurement of WC has a similar association with MACE; therefore, from a practical point of view, a single measurement may be recommended.

5. Conclusions

In conclusion, this study reinforces the association between AO determined by WC and the risk of CVD and diabetes for men (HR = 1.76, 95% CI: 1.26–2.45) and women (HR = 1.46, 95% CI: 1.09–1.83). Furthermore, we determined WC cut-off points of 89 cm in men and 86 cm in women as the best to identify this risk. Therefore, we suggest that these values should be used in patients' comprehensive cardiovascular risk assessment in Latin America.

Data availability statement

Individual-level data will not be shared because PURE is an ongoing cohort study. Requests for aggregate data will be considered on a case-by-case basis on receipt of a reasonable request.

Ethics statement

The protocol was approved by the Fundación Cardiovascular de Colombia ethics committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

JL-L and PL-J: contributed to the conception of the paper and writing of the manuscript. AG-P, PL, DG-A, and MP-M: contributed to the literature review, acquisition of data and writing of the manuscript. DM-B and JO: contributed to data analysis or interpretation. DC, AG, SR and SY: provided critical input in clinical aspects. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Intracranial pressure waveform in patients with essential hypertension

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Background: There is a strong association between hypertension and cerebrovascular diseases, but most of the mechanistic bases to justify this correlation remains misunderstood.
Objective: To evaluate intracranial pressure waveform in long-term essential hypertensive patients with a non-invasive device, brain4care (b4c).
Methods: Cross-sectional study in patients with hypertension. Office blood pressure was measured with an automatic oscillometric device. Intracranial pressure evaluation was acquired through a strain sensor that could detect and monitor nanometric skull bone displacements for each cardiac cycle. Under normal physiological conditions, P1 is greater than P2, and the normal P2/P1 ratio is <1. Time to peak (TTP) is the measurement in seconds of the beginning of waveform inscription until P1 and normal values are <0.20 s. The cut-off points ≥1.2 and ≥0.25 s were used to define intracranial hypertension (ICHT).
Results: 391 consecutive patients were evaluated (75% female, mean age 64.3 ± 12.0 years). Mean value of P2/P1 ratio was 1.18 ± 0.25 and TTP 0.18 ± 0.63 s The obtained P2/P1 ratios were divided in three categories according to results of previous studies of normalcy (<1.0), intracranial compliance disturbance (1.0–1.19) and ICHT (≥1.2). Normal intracranial pressure was observed in 21.7% of patients, intracranial compliance disturbance in 32.7% and intracranial hypertension in 45.6%. Females showed a higher prevalence of ICHT (50.3%).
Conclusion: The prevalence of 45.6% intra-cranial hypertension in patients with long-term hypertension, particularly in women, and in those over 65 years old, emphasizes the importance of evaluate intracranial pressure behaviour in these patients and raise a question concerning the real ability of cerebral autoregulation and vascular barriers to protect the brain.

KEYWORDS

hypertension, intracranial pressure, brain vascular disorders, cerebrovascular diseases, cognitive disfunction

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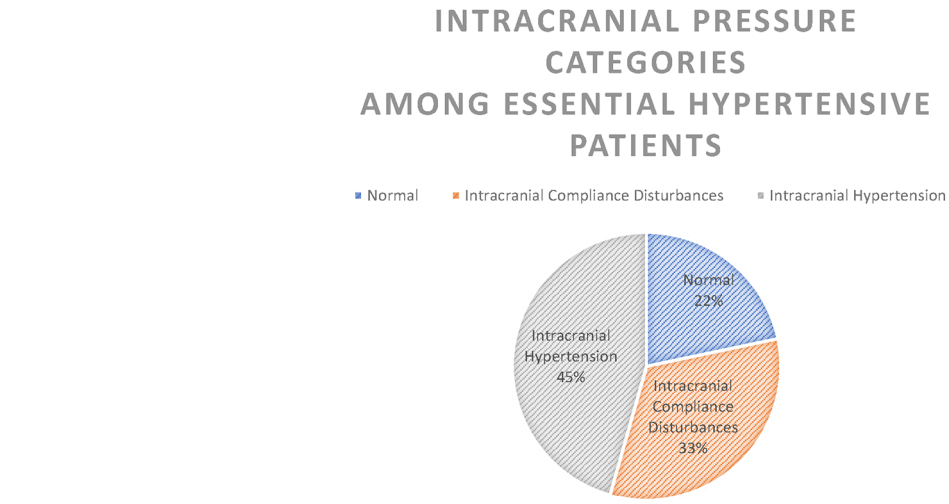

GRAPHICAL ABSTRACT

Introduction

According to World Health Organization (WHO), hypertension (HT) remains as the leading cause of death around the globe and the absolute number of hypertensive adults has doubled in the last three decades (1).

There is a strong association between HT and cerebrovascular diseases, particularly with stroke and cognitive impairment. Despite of that, most of the mechanistic bases to justify this correlation remains to be established. Clearly there is a structural and functional damage in arterial bed concomitant with a pathological increase in blood pressure (BP) but, at least by the concept of cerebral autoregulation and vascular brain barrier, tissues and vessels inside the skull should be safe in early phases of HT (2–4).

Using a minimally invasive system to monitor intracranial pressure (ICP), Mascarenhas et al. (5) showed in 2012 that Monro-Kellie doctrine of an inextensible skull after closure of the fontanels is not completely true. Since then, the non-invasive device brain4care (b4c) have been validated for monitoring intracranial pressure waveform, enabling wider use of this methodology in clinical practice (6–9).

More recently, in 2021, Fernandes et al. (10) reported that after three weeks of induced renovascular hypertension in a rat model, there was a deleterious effect on ICP dynamics compatible with intracranial hypertension.

There is a grey zone concerning ICP behaviour in chronic hypertensive patients, and very little is known on this subject. To our knowledge, this is the first report evaluating intracranial pressure behaviour in essential hypertensive patients, with the potential to bring some light to this dark side of human history concerning cerebrovascular and cognitive disorders.

Patients and methods

Selection of patients

Since November 2022 to May 2023 all adult patients seen in the Research Center for Cardiometabolic Diseases of the Hypertension Unit, Federal University of Goias, Brazil, and scheduled to perform ambulatory (ABPM) or home blood pressure measurement (HBPM) were invited to participate in the study. The study was designed as part of a cross-sectional analysis approved by the Ethic Committee, Clinical Hospital—Federal University of Goias, number 70448823.1.0000.5078 with the main objective to evaluate the behaviour of non-invasive ICP waveform in patients with sustained hypertension.

After a routine medical history and physical examination, the following parameters were obtained: age, sex, race, body mass index (BMI) in Kg/ m^2, office systolic (SBP) and diastolic (DBP) blood pressure in mmHg, previous history of any cardiovascular (CV) clinical disease, myocardial infarction (MI), stroke, dyslipidemia, diabetes (DM), length of HT diagnosis in years and number and class of anti-hypertensive drugs.

All these variables were collected the same day when intracranial pressure waveform was measured and were managed by using the REDCap electronic data capture tool hosted in Federal University of Goias.

Blood pressure measurements

Office blood pressure was measured according to the methodology recommended by the Brazilian Guidelines on Hypertension (11) with an automatic oscillometric device

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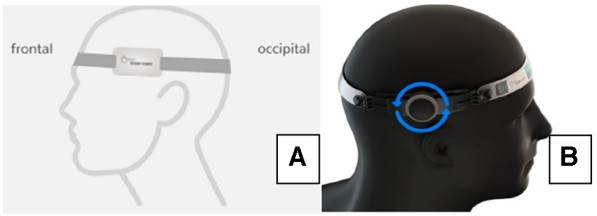

FIGURE 1
(A) Sensor placement; (B) rack adjustment.

(Omron HBP-1100). Three consecutive measurements were taken after 5 min of rest, with the patient in a sitting position, and the average of the last two measurements was recorded. By guidelines convention, controlled HT was defined when both SBP and DBP were under 140 mmHg and 90 mmHg.

Assessment of intracranial pressure

Intracranial pressure evaluation was performed in a private and silent room with patients at lying position and monitoring waveforms for seven minutes. The first and last minutes were discarded. The non-invasive device brain4care sensor was positioned on the patient's scalp and the morphology of the ICP waves was acquired through a strain sensor that could detect and monitor nanometric skull bone displacements each cardiac cycle (Figure 1).

The ICP waveform has two distinct amplitude peaks: P1 and P2. The first P1 amplitude results from transmission of systolic cerebral blood flow and P2 amplitude is associated with brain compliance to intracranial pressure (Figure 2).

Under normal physiological conditions, P1 is greater than P2, and the normal P2/P1 ratio is <1. Time to peak (TTP) is the measurement in seconds of the beginning of waveform inscription until P1 and normal values are <0.20 s. The

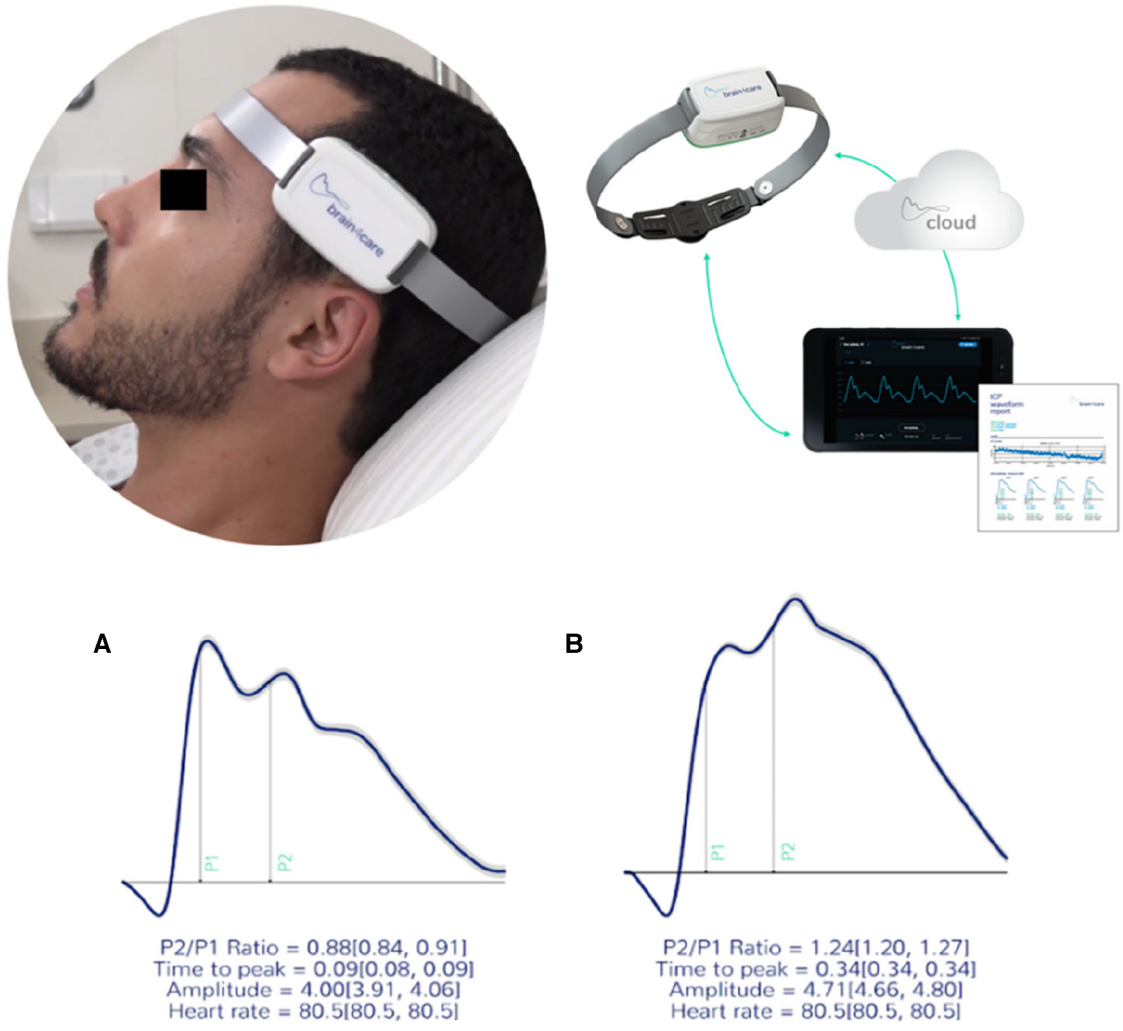

FIGURE 2
The b4c noninvasively ICP waveform real time monitoring. All data collected is immediately processed by the b4c system analytical software resulting in the quantitative and qualitative reports. (A) waveforms depicting normal standards (P2/P1 < 1.2 and TTT < 0.25 seg) and (B) altered standards (P2/P1 ≥ 1.2 and TTP ≥ 0.25 seg). (6).

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waveforms and data obtained during non-invasive ICP monitoring were automatically digitized, filtered and amplified by the device. Although intracranial hypertension (ICHT) is usually defined as a sustained (>5 min) intracranial pressure over 20 mmHg (12), using the b4c non-invasive evaluation the cut-off point identified to define ICHT by P2/P1 ratio was ≥1.2 and the cut-off for time to peak (TTP) ≥0.25 s. The values of P2/P1 from 1.0–1.19 and the TTP values from 0.20–0.24 s were considered as a grey zone of abnormal intracranial compliance but not ICHT (13–17).

Statistical analysis

Data were first recorded on the REDCap platform and exported in an excel spreadsheet format. The database was organized and cleaned, removing duplicates, and then exported to SPSS IBM version 26.0 to proceed with statistical analysis. Categorical variables were presented with their frequencies and proportions. The analysis of categorical data associations was performed using the chi-square test. Quantitative variables with data of a continuous nature were firstly analysed in terms of distribution, applying the Kolmogorov-Smirnov test; the presentation of these data was done with mean values and standard deviation when normally distributed. For the analysis of these data, parametric tests were applied, when applicable, such as the T-student test or Analysis of Variance (ANOVA).

Results

Non-invasive b4c ICP waveform was performed in 401 patients with essential long-term hypertension evaluated during a period of seven months. Ten patients were excluded due to repeated exams or inadequate quality of the signal, thus the final sample included 391 patients. The mean age was 64.3 ± 12.0 years, 75% were female, and mean BMI was 29.8 ± 6.3 Kg/m^2. The average of time since the hypertension diagnosis was 20.0 ± 12.8 years. Sociodemographic, anthropometric data and clinical variables are shown in **Table 1**.

Mean value of P2/P1 ratio of all cohort was 1.18 ± 0.25 and TTP 0.18 ± 0.63 s. The evaluation of P2/P1 and TTP behaviours in the different clinical settings as well as in the sociodemographic and anthropometric situations, did not find differences concerning P2/P1 ratio; however, TTP showed significant increased values in patients over 65 years and in those with obesity (**Table 2**).

The obtained P2/P1 ratios were divided in three categories according to the results of previous studies of normalcy (<1.0), intracranial compliance disturbance (1.0–1.19) and ICHT (≥1.2). A normal intracranial pressure was observed in 21.7% of all patients, 32.7% exhibited intracranial compliance disturbance, and intracranial pressure was observed in 45.6%. Females showed a significant higher prevalence of ICHT (50.3%). When comparing the scenarios of P2/P1 ≥1.2 and P2/P1 <1.2 females also showed a significant higher prevalence of ICHT (**Table 3**).

Discussion

The sample in our study was composed by adult patients with long-term essential hypertension with high prevalence of cardiovascular (CV) risk factors such as diabetes (41.2%) and dyslipidaemia (79.8%), and previous CV disease such as MI (11.0%) and stroke (7.4%). In addition, most of them were aged over 65 years and had overweight and obesity (**Table 1**). Despite the very well stablished association between HT and cerebrovascular diseases (ischaemic and haemorrhagic stroke) and cognitive impairment, the behaviour of intracranial pressure in these populations have not been investigated so far due to the absence of validated non-invasive methodologies. Fortunately, the validation of the non-invasive brain4care device for this purpose permits a safe and precise intracranial pressure assessment, and the investigation of the effect of short and long-term systemic hypertension on intracranial pressure waveform, contributing to a better understanding of the pathophysiology of brain damage induced by high blood pressure (5, 6).

Disturbances in blood flow delivery to the brain and blood-brain barrier (BBB) permeability seems to occur before

TABLE 1 Patient's characterization according to sociodemographic, anthropometric, and clinical variables (n = 391).

Variable	n (%)
Sex	
Female	292 (74.7)
Male	99 (25.3)
Body Mass Index (BMI) Kg/m^2	
≤18.5	3 (0.8)
18.6–25.0	80 (20.5)
25.0–29.9	138 (35.3)
≥30.0	170 (43.5)
Age group	
≥65 years	219 (56.0)
<65 years	172 (44.0)
Diabetes mellitus	
Yes	161 (41.2)
No	230 (58.8)
Myocardial infarction	
Yes	43 (11.0)
No	348 (89.0)
Stroke	
Yes	29 (7.4)
No	362 (92.6)
Dyslipidaemia	
Yes	312 (79.8)
No	79 (20.2)
Controlled hypertension	
Yes No	205 (52.4) 186 (47.6)
Length of HT diagnosis (years)	
<15 years	183 (46.8)
15–30 years	120 (30.7)
≥30 years	88 (22.5)
Number of anti-hypertensive drugs	
1 2 or 3 >3	101 (25.8) 232 (59.3) 58 (14.8)

neurodegeneration (18, 19). Disruption of BBB can occur in certain medical conditions, such as infections, inflammation or injury. When the BBB becomes compromised, it can lead to increased permeability and allow harmful substances to enter the brain that would normally be restricted to pass through. These aspects reinforce the importance of a better understanding of the role of intracranial pressure in hypertension since fluid retention, endothelial dysfunction and remodelling, of either extracranial or intracranial cerebral arteries, particularly of penetrating small vessels into the white matter, plays an important role in the pathophysiology of brain disturbances induced by changes in blood pressure (20).

We found an average value of P2/P1 ratio of 1.18 ± 0.25, and a TTP mean value of 0.18 ± 0.63 s in the whole sample of patients with hypertension, and the prevalence of P2/P1 >1.0 defining intracerebral hypertension was 78.3%. Even when using a stricter cut-off point P2/P1 ≥1.2 for ICHT the prevalence was 45.6%. The fact that at least half of the patients with long-term hypertension showed abnormal values of intracranial pressure deserves attention concerning the possibility of a lost in the capacity of cerebral autoregulation and BBB to protect brain tissue in hypertension. In opposition to what was believed, a previous publication in animal models revealed an increase in intracranial pressure just a few weeks after inducing renovascular hypertension, meaning that this injury begins in the early phases of BP elevation. The observed results in hypertensive rats and in patients with essential hypertension suggests that several concepts regarding cerebral autoregulation should be revisited (10, 21).

When we look for differences in the mean values of P2/P1 ratio and TTP in the recorded sociodemographic, anthropometric, and clinical variables (**Table 2**), the only differences observed concerned a greater TTP in elderly patients and also in those

TABLE 2 Distribution of means and standard deviations of P2/P1 ratio and TTP according to sociodemographic and clinical variables (n = 391).

Variable	P2/P1		TTP (s)	p-value
	Mean (±SD)		Mean (±SD)	
Sex				
Male	1.128 (0.229)	0.370*	0.167 (0.046)	0.467*
Female	1.192 (0.250)		0.191 (0.067)	
Age (≥65 years)				
Yes	1.151 (0.242)	0.875*	**0.207 (0.080)**	**0.001***
No	1.209 (0.249)		0.167 (0.037)	
Stroke				
Yes	1.189 (0.262)	0.267*	0.173 (0.491)	0.765*
No	1.175 (0.246)		0.186 (0.064)	
Diabetes mellitus				
Yes	1.163 (0.253)	0.899*	0.188 (0.075)	0.635*
No	1.186 (0.242)		0.183 (0.053)	
Dyslipidemia				
Yes	0.173 (0.243)	0.281*	0.184 (0.058)	0.378*
No	0.188 (0.260)		0.185 (0.064)	
BMI categories		0.119**		**0.004***
18.6–25.0	1.128 (0.249)		0.170 (0.044)	
25.0–29.9	1.194 (0.261)		0.180 (0.047)	
≥30.0	1.189 (0.231)		**0.196 (0.079)**	
Controlled HT				
Yes	1.174 (0.240)	0.735*	0.183 (0.051)	0.384*
No	1.179 (0.254)		0.187 (0.074)	
Length of HT diagnosis		0.528**		0.536**
<15 years	1.191 (0.253)		0.187 (0.055)	
15–30 years	1.167 (0.232)		0.186 (0.080)	
≥30 years	1.159 (0.252)		0.178 (0.049)	
≥30.0	1.189 (0.231)		0.196 (0.079)	
Number of anti-hypertensive drugs		0.149**		0.339**
1	1.140 (0.237)		0.177 (0.052)	
2–3	1.200 (0.252)		0.187 (0.053)	
>3	1.151 (0.236)		0.190 (0.105)	

P2/P1 ratio: ratio between P1 amplitude (resulting from transmission of systolic cerebral blood flow) and P2 amplitude (associated with brain compliance to intracranial pressure).
TTP: measurement in seconds of the beginning of waveform inscription until P1.
*t-student test.
**ANOVA.

TABLE 3 Bivariate analysis of the P1/P2 ratio according to sociodemographic and clinical variables (n = 391).

	P2/P1		
	<1.2	≥1.2	p-value
	n (%)	n (%)	
Sex			**0.002**
Female	145 (68.4)	**147 (82.1)**	
Male	67 (31.6)	32 (17.9)	
Age group			0.058
Adults	84 (39.6)	88 (49.2)	
Elderly	128 (60.4)	91 (50.8)	
Stroke			0.504
No	198 (93.4)	164 (91.6)	
Yes	14 (6.6)	15 (8.4)	
Diabetes			0.577
No	122 (53.0)	108 (60.3)	
Yes	90 (42.5)	71 (38.7)	
Dislipidemia			0.966
No	43 (20.3)	36 (20.1)	
Yes	169 (79.7)	143 (79.9)	
Myocardial infarction			0.919
No	189 (89.2)	159 (88.8)	
Yes	23 (10.8)	20 (11.2)	
BMI (Kg/m^2)			0.136
18.5–24.9	51 (24.4)	29 (16.2)	
25.0–30.0	70 (33.5)	68 (38.0)	
≥30.0	88 (42.1)	82 (45.8)	
Lenght of HT diagnosis			0.418
<15 years	93 (43.9)	90 (50.3)	
15–30 years	70 (33.0)	50 (27.9)	
≥30 years	49 (23.1)	39 (21.8)	
Controlled HT			0.707
Yes	113 (53.3)	92 (51.4)	
No	99 (46.7)	87 (48.6)	
Number of anti-hypertensive drugs			0.061
1	64 (30.2)	37 (20.7)	
2–3	11 (54.2)	117 (65.4)	
>3	33 (15.6)	25 (14.0)	

P2/P1 ratio: ration between P1 amplitude (resulting from transmission of systolic cerebral blood flow) and P2 amplitude (associated with brain compliance to intracranial pressure) transferred to the b4c system analytical software.
Chi square test.

with obesity. Considering that these differences would become apparent from the very beginning of HT, at least in animal models, perhaps a long-term exposition to high blood pressure values over years in our patients could be responsible for an important damage in the neuroprotective mechanisms (21–23). Comparing the scenarios of P2/P1 ≥1.2 or <1.2 we only found a higher prevalence of ICHT in females. Taking into consideration that stroke and dementia are more frequent in women worldwide, we can speculate that perhaps these differences in the autoregulatory capacity of intracranial pressure and BBB permeability in women, may play an important role in the pathophysiology of brain damage, although further research in this point is guaranteed (22, 24). Interestingly, P2/P1 behaviour equivalent to ICHT did not differ when comparing patients with controlled or uncontrolled hypertension, neither with the number and classes of antihypertensive drugs, highlighting once again the possibility of a loss of ability by the brain to regulate higher and lower BP ranges even under treatment with blood pressure lowering drugs (3).

Our study has some limitations; It is important to note that it is a cross-sectional analysis of the cohort, and the data related to the behaviour of P2/P1 and TTP in different subsets of patients with hypertension regarding anthropometric, sociodemographic and comorbidities may express some differences in a larger sample of subjects and, of course, that longitudinal studies are needed to evaluate other features in a cause-and-effect relationship. The strengthen of this study is to show by the first time a huge prevalence of intracranial hypertension in patients with essential hypertension and long-term exposure to high blood pressure values.

In conclusion, the observation of a prevalence of 45.6% of P2/P1 ratio over 1.2 equivalent to intracranial hypertension in patients with long-term hypertension, particularly in women, and in those over 65 years old emphasizes the importance of closely evaluate non-invasive intracranial pressure waveform in hypertensive patients. The strategy to maintaining optimal systolic blood pressure levels between 120 and 140 mmHg may help to reduce stress on blood vessels, minimizing the risk of BBB disruption. Our findings also raise a question about the accepted concept about the capacity and effectiveness of cerebral autoregulation and vascular barriers to protect the brain in the context of blood pressure elevations. This understanding can lead to a potential therapeutic avenue for hypertension-related brain complications.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comitê de Ética em Pesquisa Humana do Hospital das Clínicas da Universidade Federal de Goiás. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because Data analysis without personal identification. Noninvasive intracranial pressure waveform analysis is a routine in our unit.

Author contributions

MC: Investigation, Methodology, Writing – original draft. AS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MC: Formal analysis, Investigation, Methodology, Supervision, Writing – review & editing. SI: Formal analysis, Investigation, Methodology, Writing – review & editing. TC: Investigation, Methodology, Writing – review & editing. PV: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. PT: Conceptualization, Supervision, Writing – review & editing. GF: Conceptualization, Formal analysis, Supervision, Writing – review & editing, Software. AC: Conceptualization, Supervision, Validation, Writing – review & editing. WB: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of Interest

GF declares that he is cofounder and scientific director of brain4care. WB declares that he is Brazilian National Council for Scientific and Technological Development Researcher, Grant/Award Numbers: 313481/2020-2.

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Publisher's note

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Effect of intermediate-term firewood smoke air pollution on cardiometabolic risk factors and inflammatory markers

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Background: Temuco is a city in Southern Chile with elevated levels of air pollution (AP), mainly due to using wood as combustion throughout the cold season. The study aimed to assess the differences in cardiometabolic risk factors, estimated cardiovascular risk, and blood level of inflammatory markers between high AP (HAP) and low AP (LAP) periods.
Methods: A prospective panel study was conducted between January to September 2018. Air pollution was assessed by $PM_{2.5}$ concentration. Ninety individuals from the general population were included in the study. Measurements were performed in the HAP and LAP, including medical history and lifestyle, physical activity assessment, physical exam, and fasting blood samples for glucose, lipids, and circulatory inflammatory mediators.
Results: In the high air pollution period, systolic blood pressure was 3 mmHg higher ($p = 0.05$). HDL-cholesterol was 14.2 mg/dl lower ($p < 0.001$), Framingham risk score increased from 14.5 to 18.0 ($p < 0.001$), and highly significant lower levels of interleukins, MCP1, MMP1, MMP2, sICAM, and svCAM were observed.
Conclusions: HAP was associated with increased cardiometabolic risk factors and estimated cardiovascular risk. However, a lower level of circulating acute inflammatory molecules was observed. Inflammatory molecules blood levels were not associated with changes in cardiometabolic risk factors.

KEYWORDS
air pollution, cardiometabolic risk factors, inflammatory cytokines, cold weather, cardiovascular risk

1. Introduction

The Global Burden of Disease (GBD) study estimates that 4.2 million deaths were attributable to fine particulate material ($PM_{2.5}$) air pollution in 2015, most of them in low- and middle-income countries, where the exposure has grown significantly (1). In 2019, 70,668 deaths and 1,736,414 DALYs due to CVD were attributed to total $PM_{2.5}$ exposure in South America (2). According to GBD estimates 21% of deaths from cardiovascular disease and 24% of stroke deaths are attributable to air pollution (1). WHO has reported that 36% of deaths attributable to air pollution are due to ischemic heart disease and another 36% to stroke (3). Both acute and long-term exposure to air pollution has been associated with cardiovascular events. A systematic review reported that short-term $PM_{2.5}$ exposure increased the relative risk for acute myocardial infarction by 2.5% per 10 $\mu g/m^3$ increase (4), and another study estimated a long-term pooled effect

of an 11% increase in cardiovascular mortality for each 10 μg/m^3 $PM_{2.5}$ increase (5). The main proposed pathways linking air pollution to cardiovascular diseases are the induction of oxidative stress leading to systemic inflammation and atherosclerosis (6).

Several studies in animal models and *in vitro* have also reported that the adverse effects of PM on the cardiovascular system are by eliciting oxidative stress and inflammation (7). Oxidative stress induces endothelial function disorders, smooth muscle cell proliferation, macrophage recruitment, and inflammation, all essential factors in atherosclerotic plaque formation (8). For example, short PM exposure in elderly subjects with coronary artery disease produces elevated levels of inflammatory molecules (TNF-, Il-6, ICAM-1, VCAM-1, and P- selectin), platelet activation, and reduced levels of antioxidant enzymes Superoxide Dismutase and Glutathione Peroxidase (9). Another study in 93 elderly non-smoking adults suggested that short-term exposures to $PM_{2.5}$ pollutants (black carbon, NOx, and CO) with a high oxidative potential contribute to microvascular endothelial dysfunction (10). However, recent reports have demonstrated no clear systemic inflammatory response on controlled exposure to $PM_{2.5}$ and PM_{10}, concentrated ambient particles, or dilute diesel exhaust (11, 12).

Association between air pollution and the progression of atherosclerosis assessed through carotid intima-media thickness (13) and coronary calcium (14) have been reported. The potential mechanism for accelerated atherosclerosis may involve endothelial injury and dysfunction (15) and the worsening of cardiometabolic risk factors. Furthermore, short and long-term exposure to air pollution is associated with increased blood pressure (16–18) and elevated fasting glucose levels (19). Changes in the blood lipids profile have also been reported with long-term air pollution exposure (20, 21).

A significant contributor to air pollution in developing countries is biomass burning. This study was conducted in Temuco, a city in Southern Chile (**Figure 1**) with one of the highest levels of air pollution among American cities, mainly due to using wood as the principal combustion source throughout the cold season (April to September). PM_{10} levels were significantly associated with daily mortality and morbidity in Temuco, with older people presenting a higher risk (22). In the PURE cohort, where Temuco is one of the participant sites, the population attributable fraction for $PM_{2.5}$ was 13·9% for cardiovascular disease events, 8·4% for myocardial infarction, 19·6% for stroke, and 8·3% for cardiovascular disease mortality (23). This study aimed to assess the differences in cardiometabolic risk factors, estimated cardiovascular risk, and blood level of inflammatory markers between high air pollution (HAP) and low air pollution (LAP) periods.

FIGURE 1
Geographical location of Temuco city, Chile.

2. Materials and methods

2.1. Study design and participants

A prospective panel study was conducted between January and September 2018 in Temuco, Chile, including ninety healthy individuals older than 35 years without cardiovascular disease or recent acute infection, randomly selected from the 2,253 urban participants in the Prospective Urban and Rural Epidemiology (PURE) cohort. The Temuco-PURE study is part of an international cohort (24), selected using a random sampling stratified by socioeconomic status, assembled in urban Temuco between 2006 and 2008, that has been followed annually. The sample size was calculated assuming we will observe at least half of the increase in IL-6 reported in individuals exposed to air pollution (25). With alpha 0.05, power of 90%, a difference in IL-6 of 9.3 μm/ml, and a standard deviation of 11.5 μm/ml, a total sample size of 82 was obtained, and a 10% was added for eventual losses of follow-up. All included participants were asked to sign an informed consent, which was previously approved by Universidad de La Frontera Ethics Committee (N°042_17). Clinical and biochemical data were obtained at the end of each subject's LAP and HAP. LAP measurements were performed between January and March, while HAP measurements were performed at the end of the cold season from August to September when air pollution is significantly higher due to using firewood as combustion. Air pollution levels at LAP and HAP were

estimated using publicly available data from three monitoring stations operated by the National Air Quality Information System (SINCA) of Ministerio del Medio Ambiente, Gobierno de Chile. Monthly mean concentrations of $PM_{2.5}$ and PM_{10} from these three monitoring stations were used to represent residents' air pollution exposure. A $PM_{2.5}$ of 10 μg/m^3 was considered a limit between LAP and HAP following WHO global air quality guidelines (26).

2.2. Clinical, demographic, and laboratory measurements

Clinical measurements included questionnaires about demographics, lifestyle (smoking and physical activity), health, and medication use. Physical activity was assessed with a short version of the International Physical Activity Questionnaire (IPAQ) validated in Spanish (27). Measurements of weight, height, blood pressure, heart rate, hip and waist perimeter were obtained. Blood pressure was assessed using automatic devices following international recommendations, and the average of two measurements was recorded. The room temperature was maintained at 20°C to avoid the influence of temperature on blood pressure.

Fasting venous peripheral blood samples were drawn at the end of the LAP and HAP to obtain serum samples. Serum glucose, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, and creatinine were measured using colorimetric methods. Cardiovascular risk was estimated at each period using the Framingham equation, including age, gender, systolic blood pressure, smoking, total and HDL cholesterol, hypertension treatment, and diabetes (28). Circulating inflammatory mediators, including Interleukin (IL)-6, IL-10, IL-18, Matrix metalloproteinase (MMP)1, MMP-2, Monocyte chemoattractant protein 1 (MCP-1), soluble vascular cell adhesion molecule (sVCAM), and serum levels of soluble intercellular adhesion molecule (sICAM) were quantified using a MAGPIX® System using MILLIPLEX® MAP magnetic bead-based multi-analyte panels.

2.3. Statistical analyses

Summaries by group using appropriate descriptive statistics are provided for study variables, including demographic, clinical, and laboratory measurements. Descriptive statistics such as mean, median, standard deviation, minimum, and maximum are used to summarize continuous variables. Counts and percentages are used to summarize categorical variables. Mean values were compared between LAP and HAP periods with the paired *t*-test for continuous values. Proportions were compared by chi-square (or Fisher's exact). The effect of the medication on outcomes was assessed with stratified analyses. Correlations between clinical and laboratory variables and inflammatory markers were evaluated by the Spearman method. Statistical analyses was performed with STATA 16,1® (Statacorp, Tx. EE. UU.).

3. Results

3.1. Air pollution at high and low air pollution periods

Air pollution in 2018 assessed by $PM_{2.5}$ concentration was low between January and March, higher between April and September (the cold-weather season), and $PM_{2.5}$ concentration returned to low values after September (**Figure 2**). $PM_{2.5}$ ranges from 2.97 to 8.98 (μg/m^3) in the period of LAP sampling and between 50.39 and 63.79 (μg/m^3) in the months of HAP sampling (**Table 1**, **Figure 2**).

3.2. Clinical, demographic and laboratory measurements

Ninety individuals were included in the study; the mean age was 52 ± 10.1 years old, ranging from 36 to 75 years old. Forty-four were males, and 46 were females. Thirty-five had hypertension in treatment, 9 had diabetes mellitus, eight used statins, and 20 were active smokers.

Systolic blood pressure was 3 mmHg higher in the HAP period in the overall sample; in those without blood pressure medication, blood pressure was 117.1 ± 11.2 mmHg in the LAP period and 121.5 ± 13.3 mmHg in the HAP period ($p = 0.0024$) (**Table 2**). Total cholesterol was significantly higher in the LAP period due to higher HDL cholesterol values. In those without statin use, total cholesterol was 206.4 ± 36.0 mg/dl and 195.3 ± 43.1 mg/dl ($p = 0.0041$), and HDL cholesterol was 58.7 ± 14.6 mg/dl and 44.3 ± 13.7 mg/dl ($p \leq 0.0001$) in LAP and HAP periods respectively. Due to the difference in blood pressure and HDL cholesterol levels, the estimated 10-year risk of cardiovascular events was higher in the HAP period. No significant difference

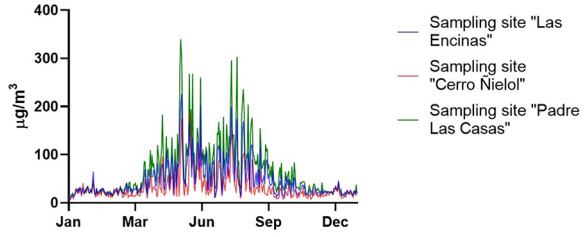

FIGURE 2
Daily PM 2.5 Concentrations in Temuco city during 2018.

TABLE 1 Monthly average of $PM_{2.5}$, PM_{10}, temperature and humidity in Temuco, 2018.

Parameter	Jan	Feb	Mar	Jul	Aug
PM 2.5 (μg/m^3)	3.61	2.97	8.98	63.79	50.39
PM 10 (μg/m^3)	23.1	20.8	21.92	71.23	57.88
Temperature (°C)	16.7	17.3	14.1	7.1	7.9
Relative humidity (%)	72.24	75	82	89	89

PM, particulate material.

TABLE 2 Mean value and standard deviation of clinical and laboratory values and 10-years cardiovascular risk estimation.

	Low AP period	High AP period	% Change	*p* value
Systolic BP (mmHg)	126.9 ± 20.1	129.8 ± 20.5	2.2	0.050
Diastolic BP (mmHg)	81.0 ± 11.6	79.8 ± 12.2	−1.5	0.31
Weight (Kg)	78.3 ± 14.6	77.9 ± 14.0	−0.5	0.24
BMI (Kg/m^2)	29.3 ± 4.6	29.4 ± 4.4	0	0.18
Waist (cm)	96.2 ± 11.6	96.0 ± 10.8	−0.2	0.50
WTH ratio	0.94 ± 0.07	0.92 ± 0.07	−0.2	0.13
Total cholesterol (mg/dl)	206.3 ± 38.9	193.9 ± 43.6	−0.06	0.0023
HDL-cholesterol (mg/dl)	58.8 ± 14.2	44.6 ± 13.4	31.8	<0.001
LDL-cholesterol	128.6 ± 30.4	123.1 ± 34.9	4.4	0.13
Triglycerides (mg/dl)	169.1 ± 113.1	140.4 ± 85.6	−20.4	0.0006
Glucose (mg/dl)	104.0 ± 35.3	102.5 ± 34.6	−1.4	0.41
METs/week	2,701.9 ± 3,336.8	3,206.9 ± 4,141.5	15.7	0.19
Framingham score	14.5 ± 13.2	18.0 ± 15.5	19.4	<0.0001

Data are reported as mean ± standard deviation, AP, air pollution; BP, blood pressure; BMI, body mass index; WTH, waist to hip ratio; HDL, high density lipoprotein; LDL, low density lipoprotein; METs, metabolic equivalents.

TABLE 3 Mean value and standard deviation of inflammatory markers in the low and high air pollution periods.

Parameter	Low AP period	High AP period	% Change	*p* value
IL 6 (pg/ml)	18.0 ± 6.4	13.3 ± 4.8	−35.3	<0.0001
IL 10 (pg/ml)	3.6 ± 0.9	2.9 ± 1.0	−24.1	<0.001
IL 18 (pg/ml)	66.3 ± 18.0	38.5 ± 18.0	−72.2	<0.0001
MCP1 (pg/ml)	178.2 ± 114.6	67.8 ± 58.7	−152.8	<0.0001
MMP1 (pg/ml)	263.9 ± 316.4	107.5 ± 145.6	−145.4	<0.0001
MMP2 (pg/ml)	945.9 ± 394.7	344.7 ± 245.0	−174.7	<0.0001
sICAM (pg/ml)	2,70,502.8 ± 1,97,273.7	1,51,436.7 ± 1,17,310.6	−78.6	<0.0001
svCAM (pg/ml)	20,011.0 ± 10,480.6	12,762.9 ± 4,934.8	−56.8	<0.0001

Data are reported as mean ± standard deviation. AP, air pollution; IL, interleukin; MCP1, monocyte chemoattractant protein 1; MMP1, matrix metalloproteinase-1; MMP2, matrix metalloproteinase-2; sICAM, serum levels of soluble intercellular adhesion molecule; svCAM, soluble vascular cell adhesion molecule.

between the LAP and HAP periods was observed in diastolic blood pressure, LDL cholesterol, or glucose levels in the overall sample and those without specific medication (Table 2). Highly significant lower levels of interleukins, MCP1, MMP1, MMP2, sICAM, and svCAM were observed during the HAP period (Table 3). Blood pressure, glucose medication, and statin use did not modify the results.

There was a moderate to high correlation between the changes observed in cytokines and a moderate correlation between cytokines changes and MMP2, sICAM, and svCAM changes. Also, changes in sICAM and svCAM were moderately correlated (Table 4). No significant correlation was observed in changes in systolic blood pressure and total and HDL cholesterol with the variations observed in inflammatory markers.

4. Discussion

Our main results are that after an intermediate exposure time, 3–4 months, of mainly wood smoke air pollution, reaching $PM_{2.5}$ mean monthly values between 50,39 to 63,79 μg/m^3, there is an increase in systolic blood pressure, a decrease in HDL cholesterol, and an increased estimated 10 years cardiovascular risk. Also, all inflammatory markers were significantly lower during the HAP period, but these changes were not correlated with the changes in cardiometabolic risk factors or estimated cardiovascular risk.

Residential wood combustion is a significant source of particulate air pollution in many countries, and biomass combustion emissions are expected to increase in the following years. In contrast, emissions from motor vehicles will decline due to improved technologies and stringent regulations, and information regarding wood smoke toxicity is limited compared to fossil fuel combustion (29). Wood smoke particles' chemical composition is different from those derived from fossil fuel combustion. Additionally, wood smoke exposures are highly variable due to the multifactorial nature of wood smoke creation (30). A comparative effect of diesel and gasoline engine exhausts, hardwood smoke, and simulated coal emissions in experimental animals concluded that all exposures caused significant results and that each could be deemed most or least toxic depending on the exposure metric used for comparison (31). There is evidence that wood smoke particles can induce an inflammatory response (32, 33) and cardiovascular events (34).

The main change in cardiometabolic risk factors in our results was the HDL-C decrease during the high pollution period, from 58 to 44 mg/dl, with an increased LDL/HDL cholesterol ratio. The Study of Women's Health Across the Nation has reported a similar effect of $PM_{2.5}$ increase, a −0.7% in high-density

TABLE 4 Correlation matrix between the changes observed in cytokines levels (pg/ml) spearman's rank correlation coefficient.

Parameter	IL 6	IL 10	IL 18	MCP1	MMP1	MMP2	sICAM	svCAM
IL 6	1							
IL 10	0.75*	1						
IL 18	0.60*	0.50*	1					
MCP1	0.31*	0.31*	0.35*	1				
MMP1	0.12	0.09	0.27*	0.42*	1			
MMP2	0.58*	0.60*	0.49*	0.25*	0.10	1		
sICAM	0.60*	0.46*	0.41*	0.17	0.15	0.51*	1	
svCAM	0.49*	0.52*	0.47*	0.35*	0.19	0.62*	0.49	1

IL, interleukin; MCP1, monocyte chemoattractant protein 1; MMP1, matrix metalloproteinase-1; MMP2, matrix metalloproteinase-2; sICAM, serum levels of soluble intercellular adhesion molecule; svCAM, soluble vascular cell adhesion molecule.
*$p < 0.05$.

lipoprotein cholesterols for each 3 μg/m^3 increase of 1-year $PM_{2.5}$ exposure (21). Also, similarly to our results, a decrease in HDL cholesterol and triglyceride levels has been reported in China (20) and in an analyses of the UK Biobank (35).

We observed an increase in blood pressure of 2.9 mmHg in systolic blood pressure and a mean difference in the $PM_{2.5}$ between LAP and HAP periods of 52 μg/m^3, without a difference in diastolic blood pressure. PM causes a systemic inflammatory response and autonomic dysfunction, which may lead to elevated blood pressure (36). A meta-analysis reported that increases in ambient $PM_{2.5}$ by 10 μg/m^3 are associated with 1–3 mmHg elevations in systolic blood pressure (16), a higher magnitude than the one we observed in our participants. However, in another meta-analysis that assessed the combined estimate of studies with a panel design, excluding cross-sectional studies, the reported increase in systolic blood pressure was lower, 0.961 mmHg (95% CI 0.497–1.426) (17), a study performed in Barcelona reported a rise of 1.37 mmHg 24-h DBP and 1.48 mmHg daytime DBP for each increase of 10 μg/m^3 of PM_{10} (37) and other studies did not find an association (38). While it has been reported an effect of temperature on blood pressure in our study, indoor temperature was set to 20°C throughout the year, reducing changes due to lower winter temperatures (39).

We did not observe differences in blood glucose levels between the LAP and HAP periods. Studies have found that ambient particulate affects fasting blood glucose. However, the results are not consistent. In a recent meta-analysis, fasting blood glucose increased 0.23 mmol/L per 10 μg/m^3 of increased $PM_{2.5}$ after long-term exposure and 0.08 mmol/L after short-term exposure (19), but in a meta-analysis restricted to cohort studies, a more appropriate study design, no association was observed between $PM_{2.5}$ levels and insulin resistance or glucose levels (40). Our results observed an increase in estimated cardiovascular risk Framingham score of 19.4%, related to the rise in systolic BP and decreased HDL cholesterol. A recent study reported an increase in daily cardiovascular mortality of 0.55% with each increase of 10 μg/m^3 in the moving average $PM_{2.5}$ in 652 cities (41). However, in our analyses, no significant correlation was observed between changes in systolic blood pressure and total and HDL cholesterol blood levels with the variations observed in inflammatory markers. This result suggests that the observed changes in blood pressure and HDL cholesterol may not be due to differences in air pollution but may be associated with changes in physical activity, diet, or lower temperatures during the HAP period.

In our study, we observed an inverse effect of $PM_{2.5}$ in circulating inflammatory mediators: IL-6, IL-10, IL-18, MMP-1, MMP-2, MCP-1, sVCAM, and sICAM levels decreased during HAP, while the production of these markers of inflammation increased during LAP. A recent meta-analysis assessed short-and long-term associations of particulate matter with inflammation markers in 44 studies. They reported significant changes in TNF-α and fibrinogen with short-term $PM_{2.5}$ exposure and no significant differences in IL-6 and IL-8 with short-term exposure. A reduction of IL-6 and IL-8 was observed in 4 of 11 and 2 of 7 studies, respectively. Long-term analyses were not possible due to limited information. A marked geographical effect was observed: IL-6 was significantly associated with PM25 exposure in Asia but not in Europe. An additional meta-regression analysis to assess the causes of results heterogeneity showed that air pollutant levels, age, study location, disease status, and study design might be the source (25).

Additionally, we must consider that our study participants were exposed to PM and other not-measured gaseous air pollutants that may influence inflammatory response. A 2022 meta-analysis analyzed the association between ozone, nitrogen dioxide, sulfur dioxide, carbon dioxide, and major inflammatory biomarkers, including IL-6 and TNF-α. They concluded that there were significant positive associations between short-term but not long-term exposure to gaseous air pollutants and inflammatory biomarkers, and several studies reported IL-6 levels reduction with air pollution (42). The differences between studies-including ours- may be explained by different PM components between countries, time, concomitant gaseous components and levels of exposure, participants' characteristics, and study design.

The strengths of our study are the sample's representativeness, since participants were a random sample of the city population, and the standardized participant measurements implemented in the PURE study. Also, the study design, where the same individual is his control, avoids potential bias. The limitations are related to the ecologic design, where exposure was not measured at the individual level and did not include indoor air pollution assessment. However, a recent study in the same city reported similar median $PM_{2.5}$ between indoor and outdoor concentrations: 44.4 and 41.8, respectively (43). Also, we did not include other air contaminant molecules described in wood smoke pollution because the information was unavailable. However, several studies have reported that they correlate well with $PM_{2.5}$ concentration (44). Our cohort study age limits, between 36 and 75 years old, exclude younger or older age individuals who may exhibit different blood pressure, cholesterol, glucose levels, or changes in cytokine levels. However, they represent an age range group where most cardiovascular events occur. Future studies must include younger individuals. Additionally, given that air pollution exposure was limited to PM2.5 and the panel design of the study, our results needs to be considered preliminary.

5. Conclusions

HAP was associated with increased systolic blood pressure, and estimated Framingham cardiovascular and decreased HDL cholesterol and inflammatory markers. The absence of correlation between the changes observed in traditional cardiovascular risk factors and cytokine levels suggests additional causal factors related to lifestyle during the cold season. Under this hypothesis, the increased event rate of cardiovascular events observed with air pollution can be the consequence of both the inflammatory effect of air pollution and the lifestyle changes that modify traditional risk factors. Health policies to control air pollution and improve traditional risk factor control should be

implemented with the aim of reducing the significant increase in cardiovascular events observed during the cold season.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Comité de Ética Científica, Servicio de Salud Araucania Sur. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization: FL, LS, and NS; methodology: FL, LS, and PS; formal analysis: FL and NS; investigation: FL, PS, NS, KS, and MH; writing – original draft preparation: FL and NS; writing – review and editing: LS, NS, KS, PS, and MH: administration: FL. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Publisher's note

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Takotsubo syndrome and atrial myxoma—identifying a new trigger: a case report

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Takotsubo syndrome (TTS) is a rare cardiomyopathy, but its prevalence is increasing due to the greater availability of diagnostic tools, whose pathophysiology is unknown; however, the evidence points to an excess of catecholamines that ends up generating cardiac stunning. The cause of excessive sympathetic discharge is multifactorial, and some tumors may be related to their origin. In this case report, we present a female patient with TTS whose only identified triggering factor was an atrial myxoma, which generated an unusual clinical presentation. Current multimodal diagnostic tools together with the multidisciplinary evaluation of the HeartTeam allowed an accurate diagnosis and an adequate management of the clinical picture.

KEYWORDS

takotsubo syndrome, atrial myxoma, multimodal imaging, HeartTeam management, case report

Introduction

Takotsubo cardiomyopathy (TTS) is a rare syndrome, with a predilection for the female sex, which usually mimics an acute coronary syndrome (ACS) and is characterized by transient ventricular systolic dysfunction (1, 2). Within its most common presentation, it exhibits akinesia-hypokinesia of the cardiac apex and medial segments, and hyperkinesia of the basal segments, with complete recovery after months (3). The pathogenesis is multifactorial, but the most likely mechanism is an excessive adrenergic discharge that generates cardiac stunning (3). Anecdotal cases of cardiac tumors, producing catecholamines, responsible for TTS, have been described (4). Among them are myxomas, the most common primary and benign cardiac tumors, typically located in the left atrium (5, 6). The association of these pathologies is extremely rare and constitutes a diagnostic and therapeutic challenge for the treating multidisciplinary team.

Case report

A 54-year-old female patient, Peruvian Andean, was admitted to the emergency department due to very intense, non-radiating oppressive chest pain, associated with nausea, vomiting and sweating and without any apparent physical nor emotional triggering factor. The patient also reported dyspnea on moderate exertion (NYHA II). As relevant medical history, she suffered a lacunar infarction in posterior limb of the left

internal capsule 3 months before admission; the patient had no other relevant personal or family pathological history. On physical examination, blood pressure was 130/77 mmHg, heart rate was 60 bpm, and SpO2 was 91% (without supplemental oxygen) so support with nasal cannula at 3 Lt/min was started, reaching an SpO2 of 96%. Skin was warm, no edema in lower limbs, capillary refill was <2 s, parvus pulse present in all 4 extremities, jugular ingurgitation was present. On auscultation, she had a low-intensity II/VI systolic murmur in the aortic focus without irradiation and fine crackles in the lower half of both lung fields. On neurological examination, the patient had mildly decreased right brachycrural muscle strength without sensory deficit or altered level of consciousness. The rest of the physical examination was normal.

Investigation

The admission electrocardiogram (ECG) showed sinus rhythm associated with ST-segment elevation in leads I, II, III, aVF, V5, V6 (Figure 1A). Therefore, the initial diagnosis of an acute myocardial infarction with inferolateral ST-segment elevation (Killip-Kimball II) was made and the patient was transferred to the cardiac catheterization laboratory. Coronary angiography revealed coronary arteries without atherosclerotic lesions (Figure 2A and Supplementary Movie S1–S5) and left ventriculography exhibited apical ballooning (Figures 2B,C and Supplementary Movie S6). Hemodynamic monitoring showed elevated left ventricular (LV) end-diastolic pressure (25 mmHg) and a pressure gradient between the LV and the aorta of 24 mmHg (see Supplementary Material). Subsequently, she was transferred to the coronary care unit for management. Transthoracic echocardiography (TTE) was performed, highlighting a characteristic contractile pattern: hypokinesia/akinesia of the apical-medial segments and hyperkinesis of the basal segments, which resulted in LV systolic dysfunction (LVEF 48%, LVEDVi 61.25 ml/m^2) (Figure 3A and Supplementary Movie S7, S8) and type II diastolic dysfunction [with elevated filling pressures (E/e' ratio 18) and left atrium dilatation (35 ml/m^2)]. Furthermore, incidentally, a mobile,

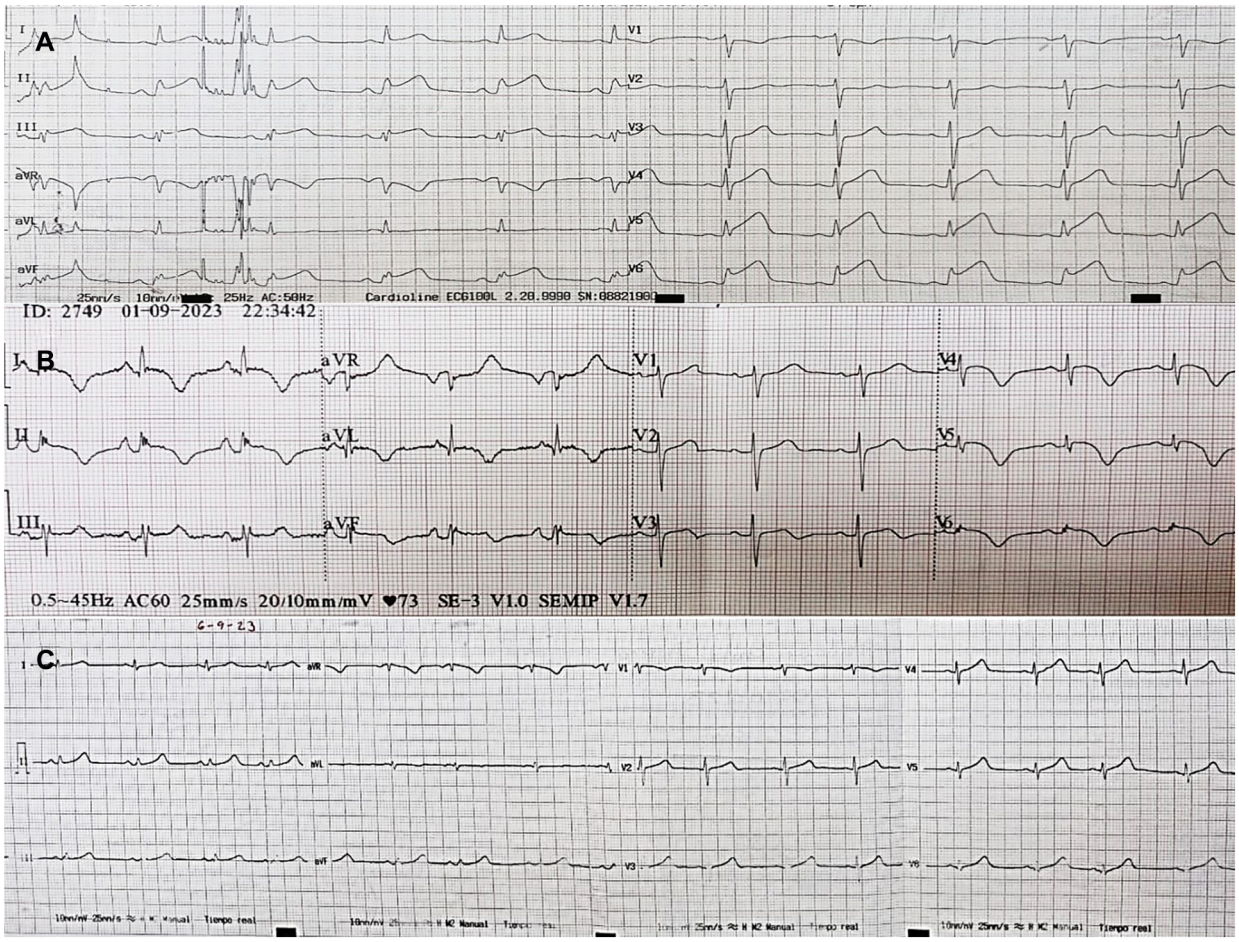


FIGURE 1
ECGs sequence. (**A**) Admission ECG: Sinus rhythm/HR 65 rpm/PR 140 ms/QRS axis +30°/QRS, 80 ms/QT 320 ms/ST segment elevation in DI, DII, DIII, AVF, V5, V6. (**B**) Day 2 ECG: Sinus rhythm/HR 70 rpm/PR 160 ms/QRS axis +30°/QRS 80 ms/QT 420 ms/negative T waves in DI, DII, aVL, aVF, V4, V5, V6/biphasic T wave V3. (**C**) Day 6 ECG: Sinus rhythm/HR 65 rpm/PR 140 ms/QRS axis +60°/QRS 80 ms/QT 400 ms/normalization of the ST segment and T waves.

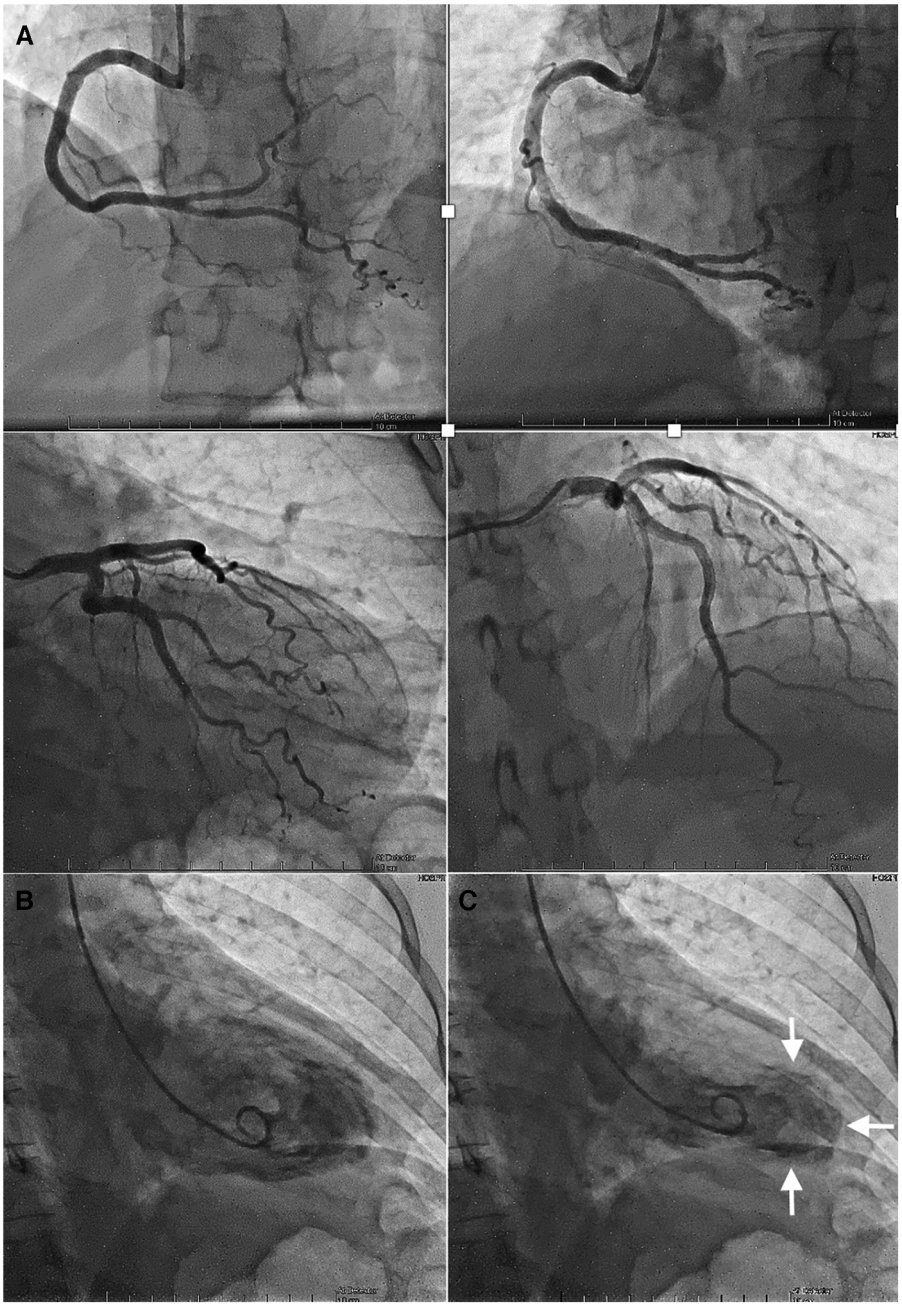


FIGURE 2
Coronary angiography and ventriculography. (A) Angiographically normal right and left coronary arteries. (B) Left ventriculography in diastole, compared to systole (C), where an apical balloon is observed (white arrows).

pedunculated, 51 × 18 mm long mass was found in the left atrium, adhered to the interatrial septum (Figure 3B). It should be noted that the intraventricular color Doppler was not turbulent. Finally, the strain analysis of the left ventricle confirmed the severe compromise of myocardial function at the apical-medial levels (Figure 3C). The cardiac computed tomography (CT) and its 3D tools better characterized the intracavitary mass, showing a bilobed, villous, 39 × 39 × 20 mm long tumor of low attenuation, and additionally demonstrated uninvolved pulmonary veins (Figures 4A–C and Supplementary Movie S9–S11). Because ischemic strokes are a recognized cause of TTS, a brain CT scan was performed to rule out a new acute ischemic embolic event. The most relevant finding was the sequel hypodensity at the posterior limb of the internal capsule. Chest CT scan showed signs of basal pulmonary congestion without the presence of consolidation or pleural effusion. Relevant laboratory tests retrospectively showed elevated troponin I 22.26 pg/ml (normal range <34 pg/ml), NT-proBNP was 625 pg/ml (normal range <125 pg/ml) and inflammatory markers were elevated with discrete leukocytosis (11,200 WBC/mm^3) with no

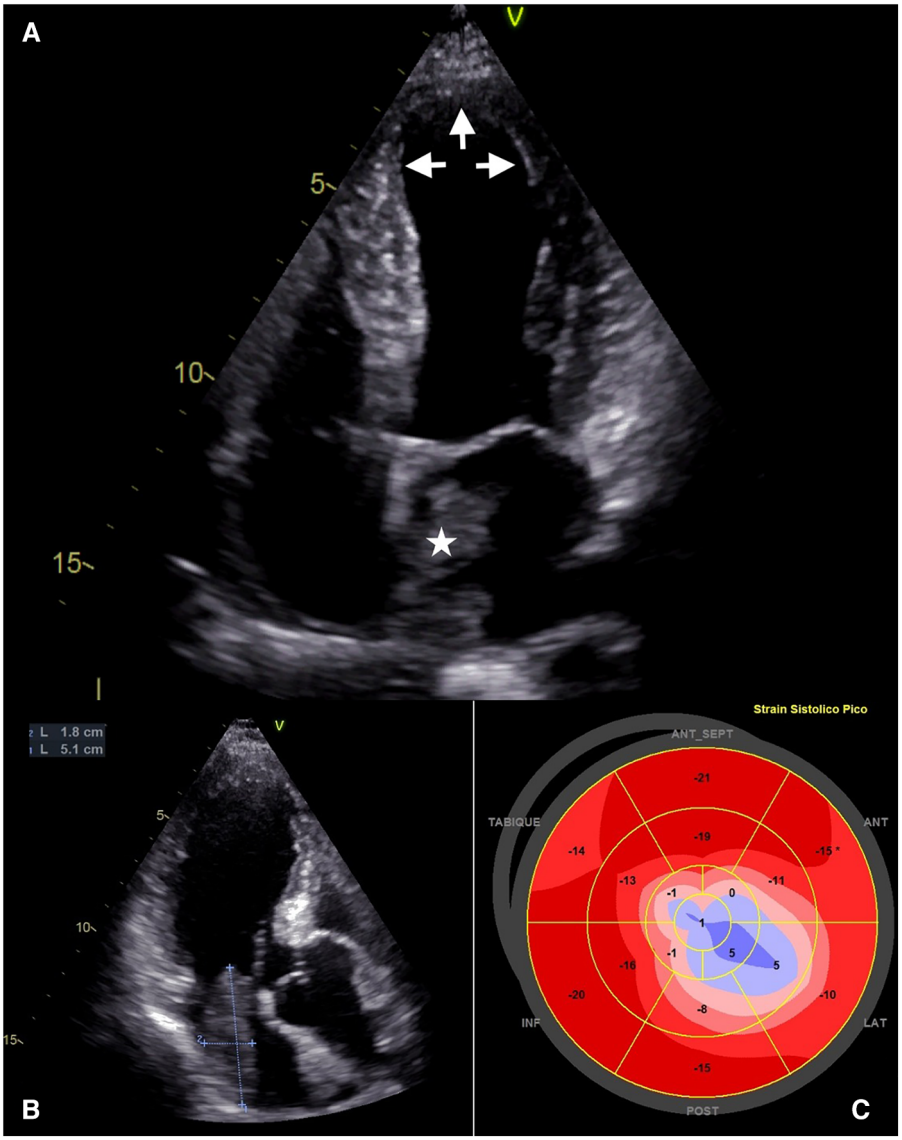


FIGURE 3
Transthoracic echocardiography. (A) TTE, apical 4-chamber view. Dilation of the ventricular cavity is seen at the apical level in systole (white arrows), and a mass is evident in the left atrium implanted in the interatrial septum. (B) TTE, apical 3-chamber view. Mass in the left atrium with a maximum diameter of 51 mm. (C) Polar map of the left ventricular strain. Illustration of apical-medial involvement and basal preservation.

left shift and a C-reactive protein value of 78 mg/L (normal range <10 mg/L), blood and urine cultures were negative and renal and thyroid function markers were normal. All these findings allow ruling out the most common triggers of TTS, supporting the hypothesis of myxoma as a precipitant of the syndrome.

Treatment

Given the findings described, the following diagnoses were proposed: TTS complicated with LV outflow tract obstruction (LVOTO), and cardiac mass, probable left atrial myxoma. The clinical picture was managed with non-invasive ventilation (high-flow nasal cannula, FiO2 50%, 50 Lt/min), high-dose loop diuretics, and complete anticoagulation with low molecular weight heparin. Forty-eight hours after admission, pulmonary decongestion was achieved and oxygenation support was progressively withdrawn. On the fifth day, the Heart Team decided the resection of the left atrial mass due to the high risk of embolization, removing a round, reddish tumor, with a villous surface, friable to the touch and measuring approximately $4.0\ cm^2 \times 3.9\ cm^2$ in length (Figure 5A). The pathological anatomy confirms the diagnosis of atrial myxoma (Figure 5B). There were no significant complications in the postoperative period and the patient was discharged early and without any problems. During hospitalization, successive electrocardiograms showed the usual course of TTS (Figures 1B,C).

At 6 weeks of follow-up, the patient remains cardiovascular asymptomatic with NYHA functional class I. Control TTE

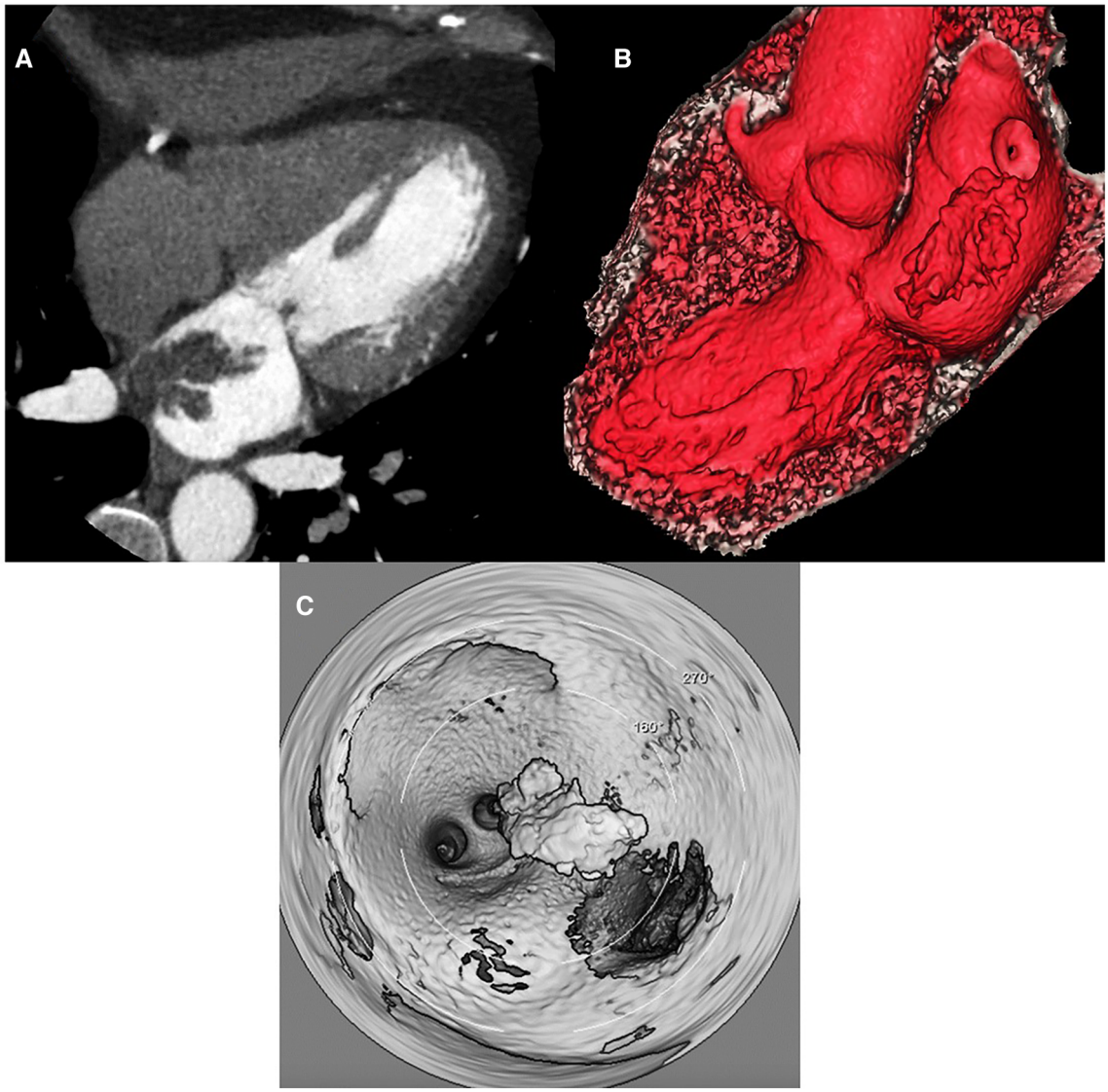


FIGURE 4
Cardiac computed tomography/3D-tools. (A) Cardiac contrast enhanced computed tomography horizontal long axis (4 – chambers) shows a lobulated, frond-like left atrial mass with villous borders (high risk of embolism), diameters of 39 × 39 × 20 mm, heterogeneous, isodense with punctate hypodense areas (clots), arising from the upper interatrial septum. (B) Oblique reformat volumen rendered 3D cardiac tomography demonstrated shows realistic anatomical relationships of left atrial mass near the ostium of the right inferior pulmonary vein. (C) Three-dimensional intracardiac navigation of 360 degrees revealed the dependence of the interatrial septum and the relationship with pulmonary veins of atrial mass.

ruled out recurrence of the mass and confirmed the normalization of LV segmental motility with recovery of LVEF (Supplementary Movie S12), which retrospectively supports the proposed diagnosis.

Discussion

Over the years and with the greater availability of different diagnostic tools, TTS diagnosis has increased worldwide (1). It is estimated that this syndrome represents approximately 2% of all patients diagnosed with ACS and approximately 10% of ACS in women (2). Typically, 90% of TTS cases occur in women, with an average age between 65 and 70 years (3, 7). On the other hand, primary cardiac tumors are extraordinary, with a frequency of approximately 0.02%, corresponding to 200 tumors per million autopsies (5). These occur more frequently in women, in a ratio of 2:1, with an average age between 50 and 60 years (6). The presence of these two pathologies is extremely rare and there are only anecdotal reports of this association (4, 8, 9). In this case report, the gender and age of the patient are correlated with the epidemiology of these two entities.

Several pathophysiological mechanisms have been proposed for the development of TTS. However, there is considerable evidence that excessive sympathetic stimulation is essential for its pathogenesis (10). Despite this, the exact mechanism by

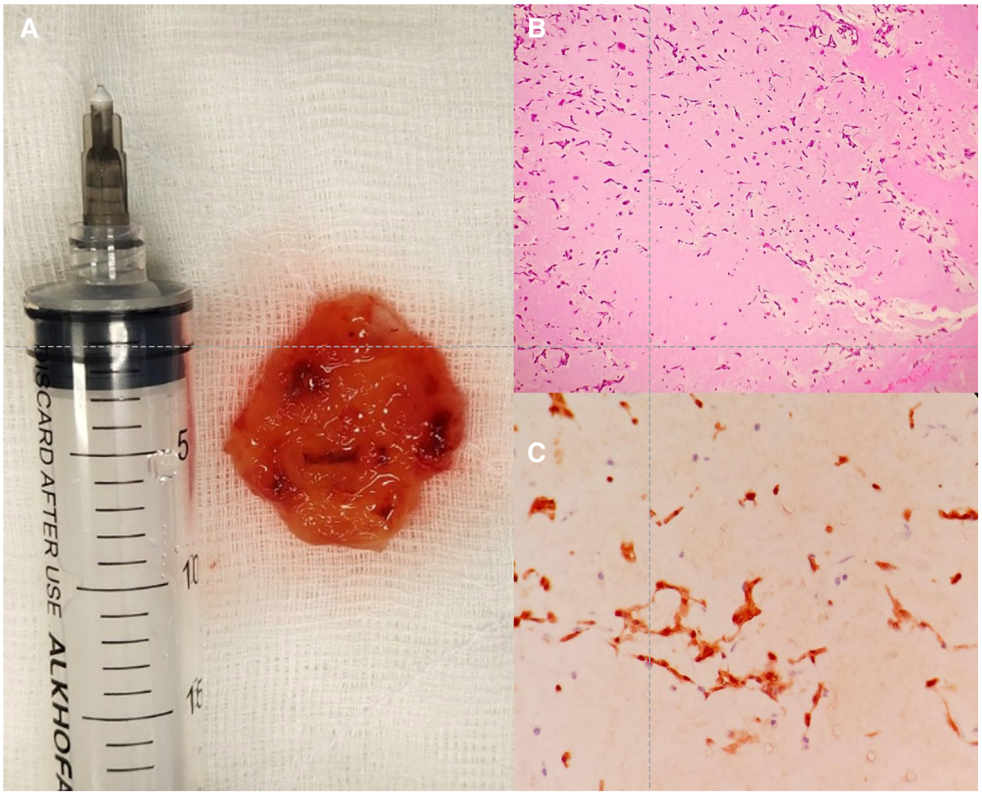
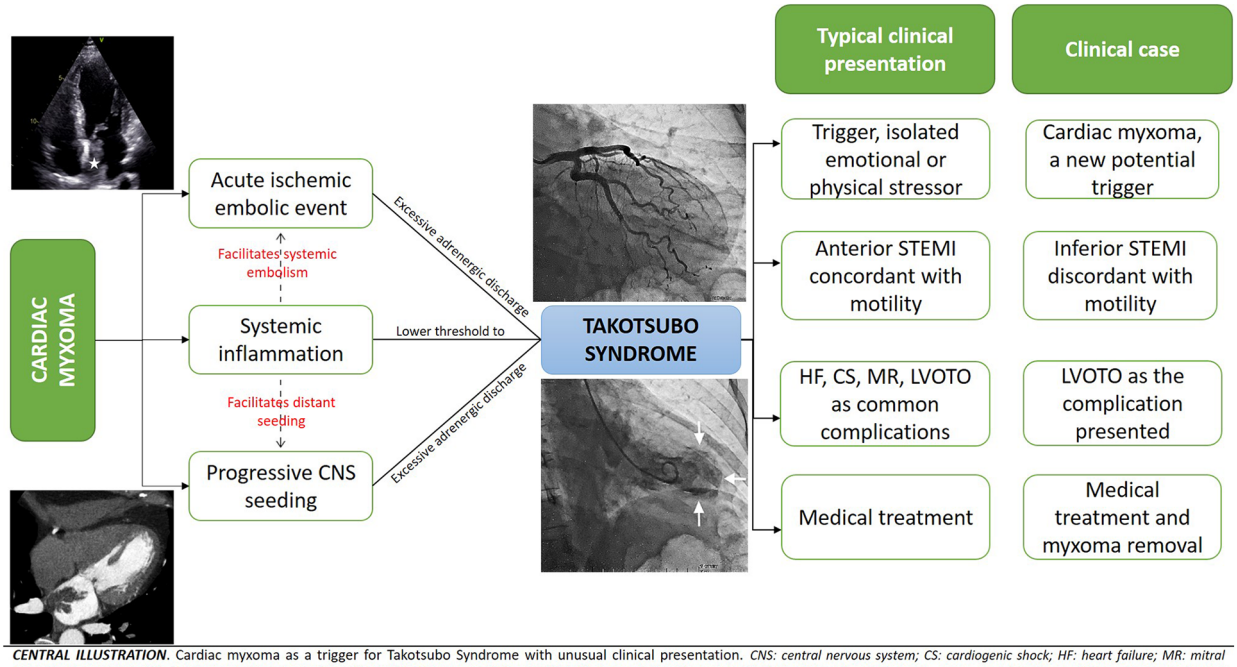


FIGURE 5
Anatomical piece and histology of the atrial mass. (**A**) Ovoid, reddish tumor, with a hairy surface, friable to the touch, approximately 4.0 cm^2 × 3.9 cm^2 in length. (**B**) Histology, stellate cells without atypia, immersed in vascularized myxoid tissue. HIM 4×. (**C**) Cells positive for calretinin staining, 10×.

which excess catecholamines precipitate myocardial stunning in different coronary territories that characterize this condition is unknown. Another fundamental characteristic of the syndrome is its relationship with stressful events as precipitants of the clinical picture (11). Various emotional or physical precipitants have been described, including cerebrovascular events and tumors. Myxomas can induce TTS through a variety of neurological (acute cerebrovascular embolism and progressive involvement of the central autonomic network through distant tumoral seeding, which can affect the cardiovascular regulation center at the CSN, generating dysregulation of the autonomic pathways and predisposing towards a more severe and persistent adrenergic discharge, which favors the development of TTS) and inflammatory mechanisms (directly triggering TTS or lowering the threshold for its development, in the context of inappropriate adrenergic discharge) (12) (CENTRAL ILLUSTRATION). Thus, we proposed atrial myxoma as the trigger of the TTS.

The clinical phenotype often mimics an acute coronary syndrome in terms of symptomatology, electrocardiographic changes, and cardiac biomarkers. The most common symptoms are chest pain, dyspnea, or syncope. However, the clinical manifestations of the acute stressor may predominate. From an electrocardiographic point of view, 98% of patients present with an abnormal electrocardiogram (44% have ST-segment elevation, 41% T wave inversion, and 8% ST-segment depression) (13). ST-segment usually involves the precordial and lateral leads (V2–V5), resembling an anterolateral infarction, while ST-segment elevation in inferior leads (II, III, aVF) is particularly rare (14). On the other hand, progressive inversion of T waves as well as prolongation of the QT interval are common electrocardiographic findings in TTS. The inversion of T waves usually occurs in the same leads with elevation of the ST-segment, although its distribution can be broader and deeper, while the long QT can be a substrate for the development of ventricular tachycardia and/or sudden death (10, 15). In our patient, the rarity of the trigger and the electrocardiographic findings of ST-segment elevation in the inferior leads differ from the usual presentation of TTS. However, all these electrocardiographic findings, together with motility disorders involving more than one arterial territory, the typical ventriculographic pattern, the complete recovery of motility defects at 6 weeks, and the presence of frequent complications of TTS supported our diagnosis.

Various complications during the acute phase of the disease can occur (cardiogenic shock, heart failure, LVOTO, mitral regurgitation, malignant arrhythmias, and embolic events) (15, 16). The latter is usually secondary to the formation of clots in the akinetic segment of the affected ventricle, associated with systemic inflammation and activation of the coagulation cascade (12). Despite this, there are no clear guidelines regarding the use of anticoagulation in the setting of atrial myxoma. Some studies suggest a lack of benefit of antiplatelet



CENTRAL ILLUSTRATION. Cardiac myxoma as a trigger for Takotsubo Syndrome with unusual clinical presentation. *CNS: central nervous system; CS: cardiogenic shock; HF: heart failure; MR: mitral regurgitation; LVOTO: left ventricular outflow tract obstruction; MR: mitral regurgitation; STEMI: ST-segment elevation myocardial infarction.* Adapted from Yalta, Kenan, et al. "Cardiac myxoma as a potential trigger of takotsubo cardiomyopathy: a brief review on mechanistic and clinical perspectives." Monaldi Archives for Chest Disease 92.1 (2022).

CENTRAL ILLUSTRATION

or anticoagulant therapy with respect to the prevention of cerebrovascular events (17), while others report favorable results with the use of anticoagulation (18). Given the mixed results and the lack of solid evidence regarding the use of these drugs, we considered that the benefit of full anticoagulation outweighed the risk, considering the short bridging time to cardiac surgery. What is more, the presence of a left atrial mass in the context of a hyperadrenergic state (with an inherent risk of atrial arrhythmias) further increases the probability of systemic embolism. Within the evaluation of the risk of systemic embolization, the use of pulsed wave tissue Doppler imaging (PW-TDI) makes it possible to determine the movement, velocity and acceleration of intracardiac masses. Those masses with a higher instantaneous velocity are associated with a greater outward force, which would increase the probability of the mass being ejected into the bloodstream. Thus, a mass peak antegrade velocity (Va) $\geq$ 10 cm/s has been proposed as a marker of embolization, allowing identification of patients at risk and timely decision making (19).

LVOTO occurs in around 20% of patients with TTS, usually due to hyperkinesis of the basal segments together with an increased interventricular septum thickness (due to underlying myocardial edema) produce high-flow velocity in a narrowed LVOT, resulting in a Venturi effect (suction effect) in the mitral valve apparatus with septal anterior motion (SAM), which generates dynamic obstruction at the level of the outflow tract. LVOTO can improve with the use of beta-blockers, however, these are contraindicated in patients with acute heart failure, hypotension, and bradycardia. Likewise, the use of nitrates in the context of acute heart failure to reduce afterload can worsen the pressure gradient and should therefore be avoided. This clearly reflects the complexity of managing a patient with TTS and its complications. The clinical consequences of TTS in our patient were mainly acute heart failure and the increased gradient of the left ventricular outflow tract. Preload optimization with loop diuretics and non-invasive ventilation were sufficient to compensate the patient and allow early surgical intervention.

Conclusions

The presence of atrial myxoma and TTS is extraordinarily rare. Different pathways can explain a cause/effect relationship between them, and the clinical presentation will depend on the underlying pathophysiological events. Coronary angiography with left ventriculography is the gold standard for the diagnosis of TTS, while multimodal imaging detects and characterizes cardiac masses. In the treatment of these concurrent pathologies, the initial objective is to stabilize the clinical picture of TTS and subsequently remove the tumor mass.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

KV-A: Conceptualization, Software, Supervision, Writing – original draft, Writing – review & editing. RS: Conceptualization, Writing – original draft. LF-Q: Conceptualization, Data curation, Software, Writing – review & editing. WA: Conceptualization, Data curation, Visualization, Writing – review & editing. RB-A: Conceptualization, Software, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2024.1323492/full#supplementary-material

SUPPLEMENTARY FIGURE
Left ventricular and aortic hemodynamic curves.

SUPPLEMENTARY MOVIE S1
LAO 45°, CRA 20° – Diagnostic Coronary Angiography – Normal right coronary circulation.

SUPPLEMENTARY MOVIE S2
RAO 30°, CRA 0° – Diagnostic Coronary Angiography – Normal right coronary circulation.

SUPPLEMENTARY MOVIE S3
RAO 25°, CAU 25° – Diagnostic Coronary Angiography – Normal left coronary circulation.

SUPPLEMENTARY MOVIE S4
RAO 15°, CRA 35° – Diagnostic Coronary Angiography – Normal left coronary circulation.

SUPPLEMENTARY MOVIE S5
LAO 40°, CAU 25° – Diagnostic Coronary Angiography – Normal left coronary circulation.

SUPPLEMENTARY MOVIE S6
RAO view – Contrast left ventriculography.

SUPPLEMENTARY MOVIE S7
TTE, 4 chambers, apical akinesia and myxoma are seen in the left atrium.

SUPPLEMENTARY MOVIE S8
TTE, 2 chambers, apical akinesia and myxoma are seen in the left atrium.

SUPPLEMENTARY MOVIE S9
Cardiac contrast enhanced computed tomography horizontal long axis (4 – chambers).

SUPPLEMENTARY MOVIE S10
Oblique reformat volumen rendered 3D cardiac tomography.

SUPPLEMENTARY MOVIE S11
Three-dimensional intracardiac navigation of 360 degrees.

SUPPLEMENTARY MOVIE S12
TTE, 4 chambers, absence of myxoma recurrence and LVEF recovery.

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The usefulness of SAGE score in predicting high pulse wave velocity in hypertensive patients: a retrospective cohort study

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Introduction: Aortic stiffness assessed by pulse wave velocity (PWV) is an important predictor to evaluate the risk of hypertensive patients. However, it is underutilized in clinical practice. We aimed to identify the optimal cutoff SAGE score that would indicate a risk PWV ≥ 10 m/s in Brazilian ambulatory hypertensive patients.
Materials and methods: A retrospective cohort study. Patients underwent central blood pressure measurement using a validated oscillometric device from August 2020 to December 2021. A ROC curve was constructed using the Youden statistic to define the best score to identify those at high risk for PWV ≥ 10 m/s.
Results: A total of 212 hypertensive individuals were selected. The mean age was 64.0 ± 12.4 years and 57.5% were female. The following comorbidities were present: overweight (47.6%), obesity (34.3%), and diabetes (25.0%). Most of the sample (68.9%) had PWV < 10 m/s. According to Youden's statistic, a cutoff point of 6 provided the optimal combination of sensitivity and specificity for identifying patients with a PWV ≥ 10 m/s. This cutoff achieved sensitivity of 97.0%, and specificity of 82.9%. In clinical practice, however, a cutoff point of 7 (where score values of at least 7 were considered to indicate high risk) had a positive likelihood ratio of 8.2 and a negative likelihood ration of 0.346, making this the ideal choice by accurately excluding patients who are less likely to have PWV ≥ 10 m/s.
Conclusion: A SAGE score ≥7 identified Brazilian hypertensive patients with a high risk of PWV ≥ 10 m/s.

KEYWORDS

hypertension, vascular stiffness, pulse wave velocity, risk prediction, blood pressure

Introduction

Pulse wave velocity (PWV) is an important tool for the early identification of vascular damage caused by elevated blood pressure (BP), or the presence of other associated factors with accelerated vascular aging (1, 2). The use of PWV as a biomarker that can gauge the overall risk of patients, identify organ damage, and facilitate clinical decision-making has

been acknowledged by guidelines and consensus documents mainly, but nonexclusively for hypertensive patients (3–5).

Carotid-femoral PWV is considered the gold-standard method for arterial stiffness, and it´s been used mainly in western countries (6). However, other methods for PWV measurement have been validated, like brachial-ankle PWV (7). Over the last years, some devices claim to estimate PWV from a single brachial cuff pressure recording, like the Cardio Mapa AOP® (Cardios, São Paulo, Brazil). By this method, central systolic BP was calculated using the ARCSolver® (Austrian Institute of Technology, Vienna, Austria) algorithm, which determines the aortic systolic BP. The aortic systolic BP can be calculated by the algorithm by two different calibration methods: C1 (using brachial systolic and diastolic BP), and C2 (using oscillometrically measured mean/diastolic BP) (8).

Despite growing evidence for the clinical applicability of noninvasive measurement of PWV (4, 9–10), its implementation in clinical practice is suboptimal and restricted to tertiary and research centers. This can be attributed to lack of regulation and reimbursement from healthcare authorities and cost of dedicated devices, among other factors (11).

The SAGE score is based on four clinical parameters (peripheral systolic blood pressure, age, fasting glucose, and glomerular filtration rate calculated by CKD-EPI) (11). It has been validated in European and Japanese populations, as well as in a Brazilian population (11–13). It has been used to screen and identify hypertensive patients with an elevated likelihood of PWV and a resulting high risk of cardiovascular events. Despite these important validation studies in hypertensive individuals, continuous efforts to validate the SAGE score throughout different communities have been made, particularly those with poor access to PWV analysis methods (12).

As such, the present study aimed to identify a SAGE score that would indicate a high risk of PWV $\geq$ 10 m/s in Brazilian hypertensive patients who had their PWV measured by an oscillometric device.

Materials and methods

This retrospective study included medical records of outpatients who consulted in a private cardiology center in Brazil. We conducted a retrospective analysis of patients who had undergone central blood pressure measurement (CBPM) using the oscillometric method from August 2020 to December 2021. The present study was approved by the Research Ethics Committee of the Federal University of Santa Maria (UFSM), RS, Brazil (CAAE 51438421.4.0000.5346) and conducted according to the Declaration of Helsinki. We included patients with 18-years-old or older with the diagnosis of systemic arterial hypertension (SAH) who consulted in the referred service. Hypertensive patients were defined as those who had high blood pressure at the doctor's office, a CBPM of ≥140/90 mmHg, or an overall mean ≥130/80 mmHg in ambulatory blood pressure monitoring (ABPM) or were using antihypertensive medications (11). The glomerular filtration rate (GFR) was estimated using the creatinine value using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Measurement of pulse wave velocity

The parameters central systolic blood pressure (SBP), central diastolic BP (DBP), peripheral SBP, peripheral DBP, PWV, and augmentation index (Aix) were obtained using a validated oscillometric device, the Dyna Mapa AOP® (Cardios, São Paulo, Brazil) (14, 15), based on triplicate measurements of PWV with C2 calibration (diastolic mean), and the data were processed with the ARCSolver® algorithm (Austrian Institute of Technology, Vienna, Austria). The measurements were performed on the left arm, with the patient in a seated position, with the legs uncrossed, feet flat on the floor, and the arm resting at heart level on a table. Patients were instructed to avoid alcohol consumption for 10 h and refrain from caffeine intake, smoking, and exercise for 3 h immediately prior to the measurement and to rest for 10 min before the procedure (16). Three readings of the central blood pressure values were obtained, and the average of the three measurements was calculated.

Calculation of the SAGE score

SAGE is the English acronym used to define the score variables: SBP, age, glucose, and estimated GFR. Each component of the acronym was categorized, and each category received a score; the SAGE score received a score from 0 to 17 points (11). After the SAGE calculation, the overall sample of hypertensive patients and those with PWV $\geq$ 10 m/s were divided into score categories from 0 to 17 to analyze the frequency of the scores. PWV values ≥10 m/s are related to increased aortic stiffness in hypertensive patients and the presence of target organ lesions (11).

Statistical analysis

The analyses were performed with the Statistical Package for Social Sciences (SPSS), version 21.0. The distribution of quantitative data was verified using the Kolmogorov–Smirnov test. The continuous variables were described as mean and standard deviation, or median and interquartile range, according to the distribution of data. Categorical variables were presented as absolute and relative values.

For each SAGE score from 0 to 17, analysis of sensitivity (SE), specificity (SP), positive predictive value (PPV), and negative predictive value (NPV) for PWV $\geq$ 10 m/s was performed, and a receiver operating characteristic (ROC) curve was constructed. The optimal cutoff point for the SAGE score to identify patients at high risk for high PWV was chosen using the Youden J index. ROC curve >0.7 was considered to indicate sufficient predictive accuracy. The cutoff point for the SAGE score was established using three criteria: higher Youden Index, sensitivity of at least 0.80 and specificity of at least 0.60. The analyses with $P < 0.05$ were considered significant.

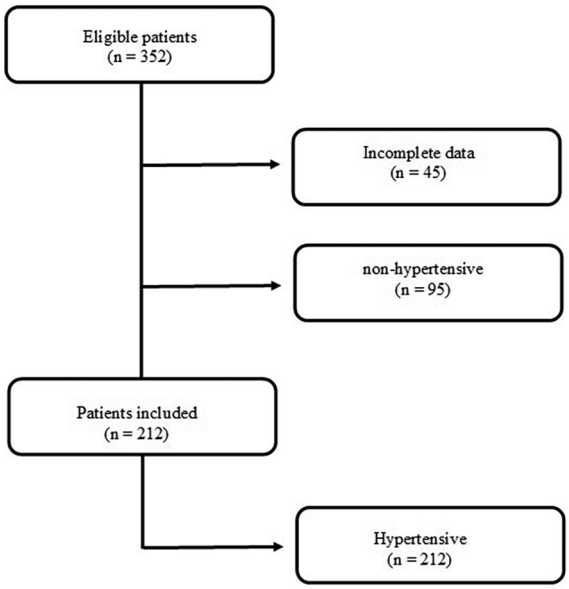

FIGURE 1
Flowchart for selection of participants. A total of 212 patients were included (diagnosed with systemic arterial hypertension).

In addition to the statistical analysis obtained by the ROC curve graph, the cutoff point was also analyzed using a qualitative approach to determine the ideal cutoff point (17).

Results

A total of 352 patient who underwent CHPM were identified. Of these, 212 were selected. Forty-five patients were excluded due to absence of clinical data necessary to calculate the SAGE score, and 95 because they were non-hypertensive (Figure 1).

The mean age of the sample was 64.0 ± 12.4 years (range 30–89 years), most often female (57.5%), overweight (47.6%) or obesity (34.3%), non-diabetic (75%) (Table 1). Most had PWV values < 10 m/s (68.9%). The performance of the SAGE score in predicting elevated PWV was analyzed. The sensitivity and specificity of different cutoff points are shown in Table 2. For the 212 patients, in the ROC analysis, the area under the curve (AUC) was 93.8% (95% CI from 90.8% to 96.8%, $P \leq 0.001$) (Figure 2).

According to Youden's J statistic, a cutoff point of 6 provided the optimal combination of sensitivity and specificity for identifying patients with a PWV ≥ 10 m/s in individuals with SAH. Table 2 shows the ability of this cutoff point in hypertensive subjects. The values were as follows: SE of 97.0%, SP of 82.9%, PPV of 71.9%, and NPV of 98.4%. For this cutoff point, a positive test is about 5.6630 times more likely to be obtained in the presence of the disease than in the absence of it. If the test with the SAGE score is negative, the likelihood ratio is 0.0366.

Despite the Youden's J statistic demonstrated the cutoff point of 6 as the optimal combination of sensitivity and specificity for identifying patients with a PWV ≥ 10 m/s, the choice of a cutoff point of 7 improved the specificity, at the expense of sensitivity. A cutoff point of 7 (where score values of at least 7 were considered to indicate high risk) had a positive likelihood ratio of 8.2 and a negative likelihood ration of 0.346. Thus, the use of this cutoff point would aid decision-making by accurately excluding patients who are less likely to have PWV ≥ 10 m/s.

TABLE 1 Sociodemographic, anthropometric, and clinical characteristics of hypertensive patients seen in a private cardiology service in the city of Santa Maria, Brazil.

Features	*N* = 212
Sociodemographic	
Age (years)	64.0 ± 12.4
Sex	
Female	122 (57.5)
Male	90 (42.5)
Anthropometric	
Weight (kg)	79.0 ± 16.4
Height (cm)	163.1 ± 21.5
Body mass index (kg/m^2)	28.7 ± 4.6
Nutritional status (BMI)	
Low weight	2 (1.0)
Eutrophic	36 (17.1)
Overweight	100 (47.6)
Obesity	72 (34.3)
Clinics	
Peripheral systolic blood pressure (SBP) (mmHg)	130.1 ± 17.5
Peripheral diastolic blood pressure (DBP) (mmHg)	82.0 ± 12.3
Central SBP (mmHg)	116.6 ± 13.9
Central DBP (mmHg)	82.8 ± 11.9
Augmentation index (Aix)	24.8 ± 10.2
Pulse wave velocity (PWV) (m/s)	9.2 ± 1.9
PWV	
<10 m/s	146 (68.9)
≥10 m/s	66 (31.1)
Fasting plasma glucose (mg/dl)	102.0 ± 22.7
Diabetes mellitus	
No	159 (75.0)
Yes	53 (25.0)
Glomerular filtration rate (ml/min/1.73 m^2)	88.9 ± 34.4
Creatinine	0.9 ± 0.2
SAGE score (median and interquartile range)	5.5 (3.3–8)

Quantitative variables with normal distribution are described as mean and standard deviation; the nonparametric variable (SAGE score), is describes in the form of median and interquartile range. Categorical variables in the form of absolute and relative values. The missing data were: one for weight; two for central SBP, and central DBP, Aix; three for height, BMI, and nutritional classification.

Discussion

In this cross-sectional study, we reported the SAGE cutoff point to identify increased PWV using a validated oscillometric device in a Brazilian population of 212 hypertensive patients. Using the quantitative approach (based on the Youden index), the cutoff point was 6. However, using a qualitative approach that prioritized achieving satisfactory PPV while maintaining a high NPV, a SAGE cutoff of 7 was chosen as the best option.

TABLE 2 Detailed report for the sensitivity and specificity of different cut points of the SAGE score in patients with hypertension from a private cardiology service in the city of Santa maria, Brazil (*N* = 212).

Cut point	Sensitivity (%)	Specificity (%)	Correctly classified (%)	+Likelihood ratio	−Likelihood ratio
>0	100	11	33.7	1.1231	0.0000
>1	100	11	33.7	1.1231	0.0000
>2	100	26	37.9	1.3519	0.0000
>3	100	36	41.5	1.5699	0.0000
>4	100	49	47.1	1.9730	0.0000
>5	100	73	62.3	3.6500	0.0000
>6	97	83	71.9	5.6630	0.0366
>7	68	92	78.9	8.2955	0.3467
>8	39	97	86.7	14.3788	0.6231
>9	30	99	90.9	22.1212	0.7066
>10	21	99	93.3	30.9697	0.7933
>11	12	100	100.0		0.8788
>12	08	100	100.0		0.9242
>13	03	100	100.0		0.9697
>14	02	100	100.0		0.9848

With this cutoff point, its emphasized that patients not selected for PWV measurement would have a low probability of PWV ≥ 10 m/s. This strategy optimizes financial resources in places with health systems that have limited PWV analysis availability (11, 13).

Our findings are similar to those reported by Tomiyama et al., who defined a SAGE cutoff point of 7 for Japanese hypertensive patients undergoing brachial-ankle PWV measurement (13). However, we reported slightly different cutoff than the one reported by Xaplanteris et al. and Oliveira et al. (11, 12). In 2019, Xaplanteris et al. validated the SAGE score using tonometry in a Greek population of patients with SAH (11). They defined the SAGE score cutoff of 8 as the best predictor of high PWV. More recently, Oliveira et al. identified the same SAGE score of ≥8 for predicting high PWV in a population of Brazilian hypertensive patients (12). In the last study, the authors measured PWV with the same oscillometric technique described in our study (12, 14, 15). The distinct cutoff observed in these studies could be related to methodological differences used to calculate the SAGE score and to measure PWV, particularly in the study by Tomiyama et al. in the last study (12, 18, 19). In the present study, the estimation of PWV was based on the Dyna Mapa AOP® oscillometric device based on its advantages and accessibility in our community (12, 14, 15). Besides it, there is a series of longitudinal studies showing a good correlation with target organ lesions and cardiovascular events with oscillometric devices (20–22), when compared to the gold standard noninvasive method of carotid-femoral tonometry (15). The differences observed between our data and the study by Oliveira et al. (12) could be related, at least partially, by regional and ethnical variations in the Brazilian population (23, 24). Additionally, the central systolic BP differences observed between C1 and C2 calibrations must also been acknowledged. Like Oliveira et al., we used C2 calibration (12). Regarding clinical validation, studies have focused on central systolic BP whereby C2 calibration is superior to cuff brachial SBP and C1 calibration in terms of association with organ damage (25–27) and mortality outcomes (27).

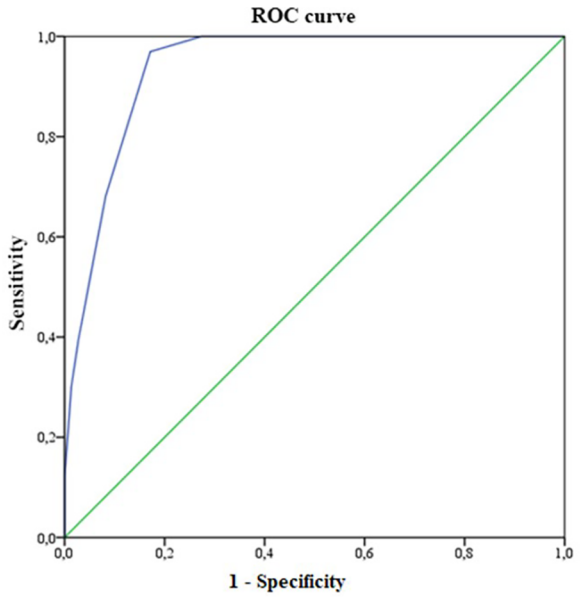

FIGURE 2
ROC curve for measuring the SAGE score in predicting cardiovascular risk (PWV ≥ 10 m/s) in hypertensive patients (*n* = 212).

The present study reinforces the importance of optimizing PWV measurement in clinical practice of patients with SAH, because this technique is still restricted to tertiary centers (2, 11). In this setting, the SAGE score becomes a simple clinical tool to identify those patients who should undergo PWV measurement. Like Oliveira et al. (12), our paper evaluated the SAGE score cutoffs against oscillometric measurements in Brazilian hypertensive patients. The present study has some limitations. First, the SAGE cutoff was obtained using data from a specific Brazilian population in south of Brazil, with mixed ethnicity (24). The sample size was small, with different ethnic background compared to the previous studies. Reference values for PWV have been defined in the Brazilian population for categories defined by age, sex, and cardiovascular risk factors

(28). However, the present study defined abnormal PWV as values greater or equal than 10 m/s, according to the original validation of the SAGE score (11).

Regarding future clinical implications, we believe that further studies with larger sample size that involves most Brazilian regions and the application of SAGE score in non-hypertensive individuals will be useful for determining the use of this score.

Conclusion

The SAGE score presented a good performance as a predictor of PWV measured in Brazilian hypertensive outpatients, using oscillometric device. The cutoff point was the same as reported in the Japanese cohort and close to that reported in the European cohort and the first published Brazilian cohort. Our data reinforce that the SAGE score is a useful and robust tool for identification of hypertensive individuals with probable PWV $\geq$ 10 m/s.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics commitee—Universidade Federal de Santa Maria. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because we designed a retrospective cohort and the ethics commitee accepted a Confidentiality Agreement Form.

Author contributions

LP: Conceptualization, Methodology, Investigation, Writing – Original Draft, Writing – Review & Editing. PC: Conceptualization, Methodology, Writing – Review & Editing, Supervision, Project Administration. EB: Investigation, Writing – Review & Editing. WB: Methodology, Writing – Review & Editing. AO: Writing – review & editing, Formal Analysis, Validation. SH: Methodology, Writing – Review & Editing. VK: Investigation. DC: Conceptualization, Methodology, Writing – Original Draft, Writing – Review & Editing, Project Administration. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Trends in primary percutaneous coronary intervention for the treatment of acute coronary ST-elevation myocardial infarction in Latin American countries: insights from the CECI consortium

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Background: ST-elevation myocardial infarction (STEMI) requires revascularization treatment, preferably via primary percutaneous coronary interventions (pPCI). There is a lack of data about contemporary management of STEMI in Latin America.
Methods: This was a multicenter, multinational, prospective, and dynamic registry of patients undergoing pPCI in Latin America for STEMI (STEMI/LATAMI Registry) that was carried out in nine centers from five countries (Argentina, Ecuador, Venezuela, Bolivia, and the Dominican Republic) between June 2021 and June 2023. All interventionalists involved in the study were originally trained at the same institution (Centro de Estudios en Cardiología Intervencionista, Buenos Aires, Argentina). The primary objective was to evaluate procedural and in-hospital outcomes of pPCI in STEMI and in-hospital outcome in the Latin America (LATAM) region; as secondary endpoints, we analyzed the following subgroups: differences between pPCI vs. pharmaco-invasive or late presenters, gender, elderly and very elderly patients, cardiogenic shock outcomes, and causes of STEMI.
Results: In total, 744 STEMI patients who underwent PCI between June 2021 and June 2023 in five countries (nine centers) in our continent were included; 76.3% had a pPCI, 8.1% pharmaco-invasive PCI, and 15.6% had late STEMI PCI. There were no differences in region or center when we evaluated in-hospital and 30 days of death. The rate of procedural success was 96.2%, and the overall in-hospital mortality rate was 2.2%. In the subgroup of pPCI, mean symptom onset-to-balloon time was 295.3 ± 246 min, and mean door-to-balloon time was 55.8 ± 49.9 min. The femoral approach was chosen in 60.5%.

In 3.0% of patients, the left main disease was the culprit artery, with 1.63 ± 1.00 stents per patient (564 drug-eluting stents and 652 bare metal stents), with 34 patients receiving only plain optimal balloon angioplasty. Definitive stent thrombosis was related to the infarct artery as the primary cause of STEMI in 7.5% of patients. The use of assistant mechanical devices was low, at 2.1% in the pPCI group. Women were older, with large numbers in very elderly age (≥90 years), greater mortality, and incidence of spontaneous coronary dissection as a cause of STEMI ($p < 0.001$, $p < 0.001$, $p < 0.001$, and $p < 0.003$, respectively).
Conclusion: In suitable LATAM Centers from low/medium-income countries, this prospective registry in patients with STEMI, PCI performed by well-trained operators has comparable results to those reported in well-developed countries.

KEYWORDS

STEMI, primary PCI, gender differences, Latin America, Caribbean, elderly

1 Introduction

Myocardial infarction is a manifestation of ischemic heart disease and constitutes a life-threatening emergency that necessitates prompt treatment, which significantly impacts the patient's prognosis. The management of this pathology follows the current classification and has shown improvement over recent decades (1). ST-elevation myocardial infarction (STEMI) denotes the thrombotic occlusion of an epicardial artery, with the current preferred strategy involving revascularization within the first 12 h of symptom onset, either through fibrinolytic agents or percutaneous coronary intervention (PCI), the latter being preferable in most scenarios (1, 2).

In its agenda for 2018–2030, the Pan-American Health Organization (PAHO) established the goal of reducing the burden of cardiovascular disease in the region. Consequently, it is imperative to assess whether the contemporary management of STEMI in Latin America is comparable to that in high-income countries (3).

In this prospective registry, we evaluated the baseline clinical and procedural characteristics, as well as in-hospital clinical outcomes of STEMI patients treated with PCI across various countries within our continent. Notably, these patients were managed by a group of interventionists trained using the same methodology.

2 Materials and methods

This was a multicenter, multinational prospective registry of patients undergoing primary percutaneous coronary intervention (pPCI) for acute myocardial infarction (AMI) in Latin America (LATAM), known as the Latin American Acute Myocardial Infarction (LATAMI) Registry. It was conducted in nine centers across five countries (Argentina, Ecuador, Venezuela, Bolivia, and the Dominican Republic) between June 2021 and June 2023. The registry embraced an all-comers approach, including all adult patients (age >18 years) who underwent pPCI, regardless of procedure success or the utilization of pharmaco-invasive or rescue PCI strategies.

The primary objective was to evaluate procedural and in-hospital outcomes, defined as a composite endpoint encompassing overall mortality, acute kidney injury, stent thrombosis, or emergent revascularization, associated with pPCI conducted in Latin American centers. Secondary endpoints involved the analysis of individual components of the primary endpoint and bleeding complications according with Academic Bleeding Consortium definitions, along with comparisons among various subgroups, including differences between pPCI vs. pharmaco-invasive or late presenters, gender disparities, outcomes in elderly and very elderly patients, outcomes in patients experiencing cardiogenic shock, and stent thrombosis as a cause of STEMI (4). In addition, in-hospital trends in complete or incomplete revascularization among patients with multivessel disease were assessed. Elderly patients were defined as those aged >75 years, while very elderly patients were those aged >90 years.

pPCI was defined as an emergent PCI to the infarct-related artery in the setting of STEMI, without prior fibrinolytic treatment, and performed within 12 h of symptom onset. The pharmaco-invasive PCI strategy was described as thrombolytic therapy combined with rescue PCI (in cases of failed thrombolysis) or systematic PCI within 2–24 h after thrombolysis.. Late PCI referred to intervention in patients with an "evolved" STEMI, presenting 12–48 h after symptom onset. Stent thrombosis was categorized as definitive or probable. Acute kidney injury was defined as an elevation of 1.5–1.9 times the baseline creatinine levels (stage 1), 2–2.9 (stage 2), or >3 (stage 3), while emergent revascularization indicated the necessity of new unplanned revascularization during hospitalization.

All interventionalists involved in the study were initially trained at the same institution (Centro de Estudios en Cardiología Intervencionista, CECI, Buenos Aires, Argentina) according to the norms and methodology of the Interventional Cardiologist Argentinian College (CACI, Colegio Argentino de Cardiología Intervencionista). The CECI group, established in 1992, comprises three Argentinian centers: Sanatorio Otamendi in Buenos Aires City; Sanatorio Las Lomas in San Isidro, Buenos Aires province; and Clinica IMA in Adrogué, Buenos Aires province. Since 2000, the CECI group has trained two interventional cardiologists every 3 years, all of whom were invited to participate in the registry, of which nine were ultimately included, as seen in Figure 1.

Data were collected from individual databases in each center, and patient information (blinded) was entered into a general online Google form with a unique ID for each patient and

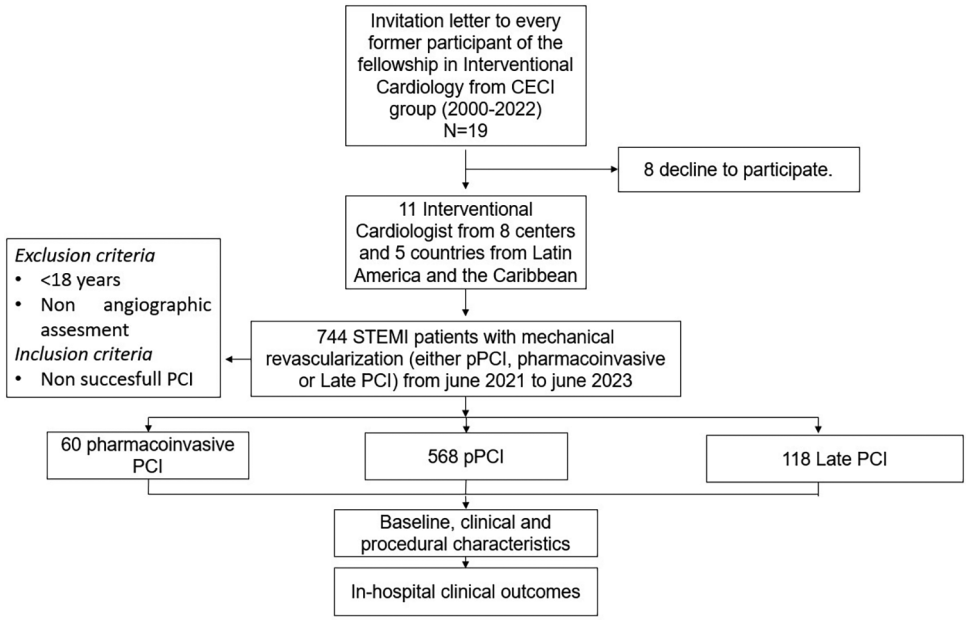

FIGURE 1
Study design. pPCI was defined as an emergent PCI to the infarct-related artery in the setting of STEMI without previous fibrinolytic treatment and within 12 h from onset symptoms. Pharmaco-invasive PCI was defined as thrombolytic therapy combined with rescue PCI (in failed thrombolysis) or systematic PCI within the first 2–24 h after thrombolysis. Late PCI was defined as the intervention in patients with an "evolved" STEMI-presenting12–48 h after symptoms initiation.

investigator. The registry protocol was presented to local authorities, approved by the Ethics Committee of the Centro de Estudios en Cardiología Intervencionista, and conducted in accordance with the Declaration of Helsinki. Patient informed consent adhered to local regulations.

Collected data encompassed demographic, clinical, angiographic, and procedural characteristics. In-hospital adverse events were also documented, with each site investigator accountable for data accuracy. All patients diagnosed with ST-segment elevation myocardial infarction who arrived at the centers and underwent pPCI were included.

Continuous variables were presented as means ± standard deviation (SD) or median [interquartile ranges (IQRs)], and categorical variables as percentages. Subgroup analysis involved age (elderly >75 years and very elderly >90 years), gender, multivessel disease, cardiogenic shock, and complete revascularization. Student *t*-tests and chi-square tests were employed to compare differences among categorical variables, while ANOVA was used for continuous variables. A two-sided *p*-value <0.05 was considered significant for all analyses. Statistical analyses were conducted using SPSS Statistics 27.0 software (IBM Corp., Armonk, NY, USA).

3 Results

3.1 Patient characteristics and clinical outcomes

In total, 744 STEMI patients who underwent PCI between June 2021 and June 2023 in five countries (nine centers) in our continent were finally included; 76.3% underwent pPCI, 8.1% underwent pharmaco-invasive PCI, and 15.6% underwent late PCI. The mean age was 63.4 ± 13.3 years, with women comprising 23.1% of the cohort. Among the entire cohort, 18.8% had a history of coronary artery disease (CAD), and 14% had experienced a previous myocardial infarction. In the pPCI subgroup, the mean symptom onset-to-balloon time was 295.3 ± 246 min, while the mean door-to-balloon time was 55.8 ± 49.9 min. The femoral approach was chosen in 60.5% of cases, including 2.7% of the initial radial approach group converted to femoral. Left main coronary artery (LMCA) disease was identified as the culprit artery in 3.0% of patients, with a mean of 1.63 ± 1.00 stents per patient [564 drug-eluting stents (DES) and 652 bare metal stents (BMS)]. In addition, 34 patients received plain optimal balloon angioplasty (POBA). Definitive stent thrombosis was attributed to the infarct artery as the primary cause of STEMI in 7.5% of patients. Multiple vessel disease was observed in 51.6% of patients, with 82.8% of them achieving complete revascularization either during the same procedure or in stages. Clopidogrel was the selected P2Y12 inhibitor in 53.5% of cases, and intracoronary IIb/IIIa inhibitors were administered in 55.4% of interventions. The comprehensive list of baseline demographic and clinical characteristics of the overall population is presented in Table 1. Clinical outcomes are detailed in Table 2, with an overall death rate of 2.2%. Procedural characteristics are outlined in Table 3.

3.2 Subgroup analyses

We did not observe any regional or center-based disparities when assessing in-hospital and 30-day mortality. However,

TABLE 1 Demographic, clinical, and procedural characteristics of the overall population ($n = 744$ patients).

Demographic and clinical characteristics	
Age (years)	63.3 ± 13.3
Symptom onset-to-balloon time (min)	295.3 ± 246
Door-to-balloon time (min)	55.8 ± 49
Male gender (%)	76.9
High blood pressure (%)	58.3
Dyslipidemia (%)	44.9
Current smoker (%)	23.7
Diabetes (%)	23.4
Family history of CAD (%)	10.5
Known CAD (%)	18.8
Previous myocardial infarction (%)	14.0
Previous revascularization procedure (%)	13.7
Previous PCI (%)	12.6
Previous CABG (%)	1.9
Procedural characteristics	
Primary PCI (%)	76.3
Pharmaco-invasive PCI (%)	8.1
Late PCI (%)	15.6

; CABG, coronary artery by-pass surgery.

TABLE 2 Procedural and in-hospital outcomes ($n = 744$ patients).

Overall death (%)	2.2
Stent thrombosis (%)	2.6
Acute kidney injury (%)	2.4
Emergent revascularization (%)	2.6
Composite ischemic primary endpoint (%)	6.9

TABLE 3 Procedural characteristics of the overall population ($n = 744$ patients).

Procedural characteristics	
Primary PCI %)	76.3
Pharmaco-invasive PCI (%)	8.1
Late PCI (%)	15.6
Femoral access (%)	60.5
Infarct-related artery	
Left main (%)	3.0
Left arterial descendent artery (%)	50.5
Saphenous vein graft (%)	0.5
Multiple vessel disease (%)	51.6
Spontaneous coronary artery dissection (%)	0.5
In-hospital complete revascularization (%)	49.5
Programmed complete revascularization (%)	82.5
In-stent thrombosis (%)	7.5
Patients with DES implantation (%)	44.6
Patients with BMS implantation (%)	47.3
Patients with both DES and BMS implantation (%)	3.5
POBA (%)	4.6
N stent per patient	1.63 ± 1.0
Clopidogrel (%)	53.5
TIMI thrombus grade 0 or I (%)	77.9
No reflow (%)	7.8
Intracoronary IIb/IIIa inhibitors (%)	55.4
Manual thrombectomy (%)	18.3
Contrast (ml)	188 ± 65
Procedural success (%)	96.2

discrepancies were noted concerning the type of PCI (primary, pharmaco-invasive, and late), with a higher prevalence of the latter observed in less populated areas, as illustrated in Figure 2.

3.2.1 Primary PCI

In the subgroup analyses, there were no significant age differences between patients who underwent pPCI and those who did not, with mean ages of 64.5 ± 13.4 and 62.8 ± 12.5 years, respectively ($p = 0.12$). However, there was a trend toward a higher proportion of primary interventions in men compared to women (78.0% vs. 70.9%, $p = 0.057$). Of note, there was a significant difference between non-diabetics (78.9%) and diabetics (67.8%) in terms of pPCI utilization ($p = 0.002$). Although there were no significant differences observed in previous history of myocardial infarction ($p = 0.17$), a significantly higher number of patients underwent revascularization in the pPCI group compared to late presenters (87.2% vs. 12.8%, $p = 0.004$).

Newer 2PY12 inhibitors (prasugrel and ticagrelor) were preferred over clopidogrel in the primary PCI group (54.1% vs. 19.3%, $p < 0.001$), and the femoral approach was the predominant access route (69.4% vs. 31.8%, $p < 0.001$).

In the pPCI group, LMCA disease was identified as the culprit artery in a higher proportion compared to non-primary PCI procedures (3.5% vs. 1.1%, $p = 0.07$). In addition, a greater number of stents were deployed in non-primary PCI procedures (1.82 ± 1.1 vs. 1.57 ± 0.94, $p = 0.03$), and although there were no differences in terms of TIMI 0–1 flow nor no-reflow phenomena in the infarct artery ($p = 0.43$ and $p = 0.11$, respectively), the use of thrombus-aspiration devices was significantly higher in the pPCI group (20.6% vs. 11.4%, $p = 0.006$) as was the intracoronary administration of IIb/IIIa inhibitors (13.2 ± 7 vs. 10.0 ± 2.3 ml, $p < 0.001$).

Contrast use was statistically higher in the pPCI subgroup (194 ± 64 vs. 173 ± 67 ml, $p < 0.001$). Although no significant differences were observed in overall death ($p = 0.28$) or cardiogenic shock ($p = 0.53$), the utilization of an intra-aortic balloon pump (IABP) was significantly higher in favor of pPCI (2.1% vs. 0.0%, $p = 0.03$) as was the use of a transient pacemaker (4.6% vs. 1.1%, $p = 0.02$). No intravascular imaging was used during the initial procedure.

3.2.2 Gender differences

In comparing men and women, women were older, with mean ages of 71.7 ± 14.3 vs. 62.6 ± 12.5 years for men ($p < 0.001$). Similarly, the prevalence of high blood pressure was significantly higher in women compared to men (75.4% vs. 50.7%, $p < 0.001$). Men exhibited a higher incidence of coronary artery disease history (22.0% vs. 8.2%, $p < 0.01$), with a trend toward a higher incidence of previous AMI (14.3% vs. 8.2%, $p = 0.074$). As expected, men had a higher prevalence of previous revascularization (16.1% vs. 8.2%, $p = 0.027$), while women had a higher incidence of previous stroke (2.2% vs. 6.6%, $p = 0.01$).

The femoral approach was more commonly used in women compared to men (77.0% vs. 67.3%, $p = 0.03$), although there was no significant difference in the conversion rate from radial to femoral ($p = 0.5$). Women had a higher prevalence of LMCA

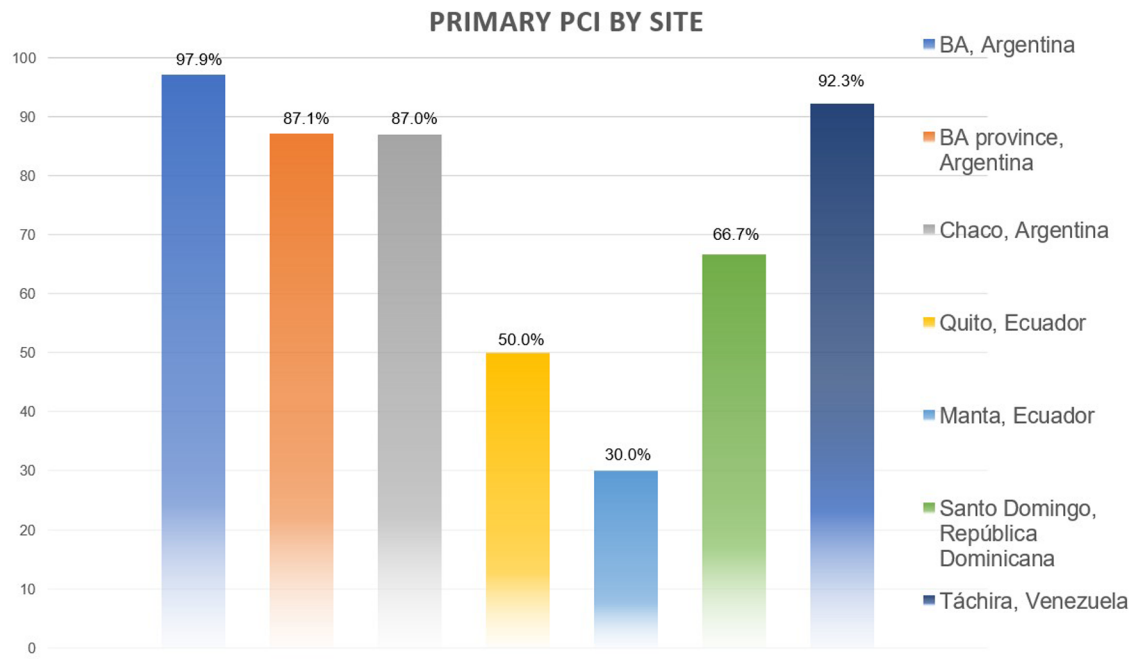

FIGURE 2
Differences in primary PCI access between regions.

disease (6.6% vs. 2.7%, $p = 0.04$) and spontaneous coronary artery dissection (2.3% vs. 0.0%, $p = 0.003$). Definitive stent thrombosis as the cause of STEMI was more prevalent in men compared to women (9.0% vs. 3.3%, $p = 0.023$), while clopidogrel was more commonly prescribed for women (54.1% vs. 42.6%, $p = 0.24$). However, the administration of IIb/IIIa inhibitors tended to be higher in men (50.0% vs. 59.5%, $p = 0.06$), although neither TIMI 0–1 flow ($p = 0.36$) nor non-reflow phenomena ($p = 0.81$) differed significantly between the two groups.

Overall, in-hospital mortality was significantly higher in women compared to men (6.6% vs. 1.3%, $p = 0.001$), with a numerically higher incidence of cardiogenic shock in women (8.2% vs. 4.9%, $p = 0.12$), although no IABP was utilized in the women's group (0.0% vs. 2.7%, $p = 0.053$).

Notably, men presented with multiple vessel disease more frequently than women (53.4% vs. 39.3%, $p = 0.006$), and a higher proportion of men underwent complete revascularization during baseline hospitalization compared to women (31.1% vs. 16.7%, $p = 0.044$).

3.2.3 Age

In terms of the elderly population, consisting of 170 patients aged >75 years, and the very elderly population, comprising 56 patients aged >90 years, compared with the rest of the cohort, notable differences were observed.

In the first subgroup, the mean age was 81.9 ± 5.9 years, significantly higher than that of the rest of the population (58.8 ± 9.7 years, $p < 0.001$). Younger patients demonstrated shorter symptom onset-to-balloon times compared to the elderly (median 276 vs. 356 min, $p = 0.003$), although there were no disparities in door-to-balloon times ($p = 0.50$). A higher proportion of women was observed in the elderly subgroup ($p < 0.001$), along with a higher prevalence of known coronary artery disease (27.1% vs. 16.6%, $p = 0.002$) and stroke (9.4% vs. 0.7%, $p < 0.001$). The femoral approach was more frequently employed in the elderly group (74.1% vs. 56.2%, $p < 0.001$), and there was a higher incidence of multiple vessel disease (58.8% vs. 50.2%, $p = 0.048$), although there were no differences in complete revascularization during index hospitalization ($p = 0.45$). Clopidogrel was the preferred choice in the elderly subgroup (75.3% vs. 47.3%, $p < 0.001$), with no significant differences in overall mortality (2.4% vs. 2.1%, $p = 0.85$).

In the very elderly subgroup, the mean age was 89.1 ± 3.9 years, significantly higher than the rest of the cohort (62 ± 11.5 years, $p < 0.001$). This group exhibited a numerical trend toward worse symptom onset-to-balloon times (353 ± 196 vs. 289 ± 250 min, $p = 0.13$) and significantly worse door-to-balloon times (median 78.3 vs. 54 min, $p = 0.004$). A higher proportion of women were also noted in this group (60.7% vs. 39.3%, $p < 0.001$). Notably, none of the very elderly subgroup were smokers ($p < 0.001$). The femoral approach was more frequently utilized in the very elderly group (82.1% vs. 58.5%, $p < 0.001$), with a higher incidence of left main coronary artery involvement as the infarct artery (7.1% vs. 2.6%, $p = 0.058$). The administration of IIb/IIIa inhibitors was more common in the non-elderly group (56.8% vs. 39.3%, $p = 0.01$), with no significant differences in non-reflow phenomena between the groups.

3.2.4 Other subgroup's clinical outcomes

We assessed in-hospital overall mortality as the primary clinical outcome in the 44 patients who developed cardiogenic

shock, revealing a significantly higher incidence of death in this subgroup compared to the general population (22.7% vs. 0.9%, $p < 0.001$). The presence of LMCA involvement as the infarct artery (18.2% vs. 2.0%, $p < 0.001$) and TIMI 0–1 flow (95.5% vs. 78.9%, $p = 0.003$) were also associated with this cohort of patients, whereas there were no significant associations found with stent thrombosis ($p = 0.33$), multiple vessel disease ($p = 0.39$), or age (62.6 ± 12.9 vs. 62.2 ± 13.2 years, $p = 0.45$). Trends were observed regarding gender, with 31.8% of women in the cardiogenic shock group ($p = 0.11$), and the incidence of no-reflow phenomenon (13.6% vs. 7.4%, $p = 0.11$).

Subgroup outcomes are presented in Supplementary Table S1 and Figure S3.

3.2.5 Bleeding complications

We did not encounter any major bleeding events in our series, and overall bleeding rate was 6.3% for any type of bleeding. Detailed in-hospital and periprocedural bleeding complications according to the Bleeding Academic Research Consortium (BARC) classification are provided in Supplementary Table S2 (4).

4 Discussion

To the best of our knowledge, this is the first prospective registry in Latin America assessing the clinical outcomes of ST-elevation myocardial infarction treated with PCI performed by interventionalists trained at the same center.

The Centro de Estudios en Cardiología Intervencionista was established over 20 years ago to promote medical education and academic activities. Since then, more than 25 interventional cardiologists from Argentina and Latin America have completed the fellowship program at our institution. This fellowship is part of the CACI interventional cardiology program, affiliated with the Buenos Aires University. To the best of our knowledge, this is the first report to consider the impact of interventionists' training location on patient outcomes.

According to a review by Alves et al., in-hospital mortality rates for STEMI patients in Latin America have varied widely across studies, ranging from 4.9% to 17.5%. However, there is a lack of data regarding the number of patients treated with primary PCI who died within the first 30 days (5). Similarly, in Europe, overall mortality rates have shown significant regional variation, ranging from 4.9% to 10.8%, with limited information available on the success of pPCI as a reperfusion therapy (6). In our registry, the in-hospital mortality rate was 2.2%, likely influenced by a shorter door-to-balloon time (55.8 ± 49.9 min), with 90.5% of patients receiving pPCI within 90 min. This contrasts with findings from a multicenter registry in Argentina, where only 30% of STEMI patients received pPCI within 90 min, resulting in a higher in-hospital mortality rate of 7.7%. However, our results align closely with those of the nationwide registry from Norway (NORMI), which reported an in-hospital mortality rate of 3% (7, 8).

The ISAC-STEMI COVID-19 Registry (The International Study on Acute Coronary Syndromes–ST-elevation myocardial infarction), a multinational collaboration from high-volume centers during the COVID-19 pandemic, provided insights into the treatment and outcomes of STEMI patients, reporting a median door-to-balloon time of 40 min (with 70% within 60 min) and an in-hospital mortality rate of 3.9% in 2019 (7–9). Similar findings were observed in a contemporary meta-analysis, where pPCI demonstrated an in-hospital mortality rate of 4.8% (9). During the COVID-19 pandemic, we did not analyze outcomes based on COVID-19 positivity in STEMI patients or investigate differences related to night shifts.

Since the COMPLETE Trial (Complete vs. Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early PCI for STEMI), current guidelines recommend complete revascularization as the standard treatment for patients with STEMI and multivessel disease, excluding those with cardiogenic shock (1–12). In our trial, we report a complete revascularization rate of 82.8%.

There are relevant data in the subgroup analysis, and despite being hypothesis generators, it is important to highlight them since there is a lack of contemporary data from the region (7, 13, 14).

The subgroup analysis provides relevant data, and despite being hypothesis generators, it is important to highlight them due to the lack of contemporary data from the region (7, 13, 14).

When we analyzed the subgroup aged >75 years, we found significant differences in symptom onset-to-balloon time ($p = 0.003$) compared to younger patients, while there were no differences when we compared door-to-balloon times ($p = 0.50$). This underscores the need for better communication and awareness with this population, taking into account that this subgroup had a larger history of coronary artery disease ($p = 0.002$), cerebrovascular accident ($p < 0.001$), and multiple vessel disease ($p = 0.048$), indicating previous contact with the healthcare system and secondary prevention. Even though this subgroup had a higher risk profile, there were no differences in complete revascularization during index hospitalization or in-hospital mortality compared to the younger cohort (15–17).

In the cohort of patients aged >90 years, there were worse door-to-balloon times, and they had more complex lesion morphology, with more LMCA involvement ($p < 0.001$). However, cardiogenic shock and in-hospital mortality did not differ, highlighting the importance of pPCI in this subgroup (18).

The rate of in-stent thrombosis as a cause of STEMI was 7.5% in our cohort, slightly higher than the incidence of 5.1% found in elderly patients in the worldwide ISAC-STEMI COVID-19 Registry (9). Given that none of them were due to an acute event, the lack of intracoronary imaging in our series did not allow us to assess the pathophysiology of stent thrombosis. Nonetheless, the occurrence of stent thrombosis as a cause of STEMI at rates of 5%–7.5% appears higher than expected with current stent designs and warrants further analysis. Although direct assessment of antithrombotic therapy in patients requiring oral anticoagulation for atrial fibrillation was not conducted, clopidogrel emerged as the most commonly used antiplatelet agent ($p < 0.001$). This preference may be justified by the higher costs associated with new antiplatelet agents in the Latin American region.

The number of BMS implanted in the registry is higher than in other series, which could be attributed to economic restrictions in certain regions of Latin America. However, despite these

differences, there is no evidence of disparities in overall death or myocardial infarction between BMS and DES, as indicated by contemporary meta-analyses. Our findings align with this trend, showing no significant differences among stent selections ($p = 0.42$) (10–12). The intracoronary use of IIb/IIIa inhibitors was prevalent in the overall population (55.4%), with an average bolus dose of 12 ± 6 ml per patient, administered in 61% of the 580 patients with TIMI thrombus grade 0 or 1. Notably, we did not observe higher mortality in this subgroup (2.0%), which is consistent with previously published evidence from our group and other researchers (19–21). When we analyzed women, we observed similar differences to those reported in previous registries. Women tended to be older and have higher blood pressure, and clopidogrel was the preferred P2Y12 inhibitor (22, 23). As expected, spontaneous coronary artery dissection was more common in women, consistent with current evidence (24). Although there were no differences observed in TIMI flow or no-reflow, women received fewer IIb/IIIa inhibitors, and in-hospital mortality was higher ($p = 0.001$). The main findings from the gender comparisons are presented in Supplementary Table S1. In summary, there remains a treatment gap for STEMI in women, highlighting the need for dedicated programs and protocols to address these gender differences (25). Unlike other registries, all participating centers had a high volume of procedures (range of 840–1354). Therefore, analyses were not conducted to assess the relationship between operator volume and procedure-related mortality (26).

The rate of 30-day mortality in patients with cardiogenic shock is lower (23%) than that reported in previously major randomized clinical trials but similar to those in current national registries (43% and 28%, respectively) (27, 28). The small sample size, similar trained skills among operators with the PCI policy of culprit artery treatment only in cardiogenic shock, and short follow-up period could explain these findings.

Although previous studies have reported an association between coronary perforations and the incidence of the no-reflow phenomenon, we did not observe such an association in our study (29). Despite the high rate of femoral approach in our patient cohort, major bleeding events were not observed, with only 1% of patients experiencing bleeding requiring intervention, and an overall bleeding rate of 6.3%.

In the ORPKI Polish National Registry, Siudak et al. reported a decrease in mortality and bleeding with the radial approach (30). However, in our registry, the incidence of bleeding was not elevated, potentially due to operator preferences. Previously, our group published results from a patient series showing a numerical but not statistically significant difference in minor vascular events favoring the radial approach, including pseudoaneurysms managed conservatively (31).

5 Limitations

We identify limitations in our registry. First, these findings cannot be generalized to all centers in Latin America, although results among the participating centers were similar.

Second, the low utilization of mechanical assistant devices, such as IABP and Impella, compared to registries in more developed regions may reflect inequities and the burden of poverty in certain areas of the region; however, in-hospital mortality was comparable to other series. Nevertheless, the efficacy of these technologies during pPCI is controversial, potentially adding cost without clear benefit (28, 32).

Finally, we did not conduct a multivariate analysis to avoid drawing conclusions from a cross-sectional registry with numerous unmeasured biases. Instead, comparisons were made to identify potential caveats.

6 Conclusion

Our study has demonstrated that the outcomes of PCI for patients with STEMI in developing countries, when performed by well-trained operators, are comparable to those observed in developed countries with higher resources. This finding underscores the pivotal role of specialized training in bridging the gap in cardiac care quality between developed and developing nations. It proves the necessity for well-structured programs dedicated to training more interventional cardiologists. Such initiatives are essential for maintaining the highest standard of care for patients in these regions.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The requirement of ethical approval was waived by Centro de Estudios en Cardiologia Intervencionista for the studies involving humans. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AR-G: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. LS: Investigation, Writing – review & editing. GP-O: Investigation, Writing – review & editing. DA: Investigation, Writing – review & editing. HP: Investigation, Writing – review & editing. RG-V: Investigation, Writing – review & editing. IB: Data curation, Writing – review & editing. FF: Data curation, Writing – review & editing. JP: Data curation, Writing – review & editing. JG: Data curation, Writing – review & editing. JM: Data curation, Writing – review & editing. FC: Data curation, Writing – review & editing. CF-P: Data curation, Writing – review & editing. AR: Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2024.1275907/full#supplementary-material

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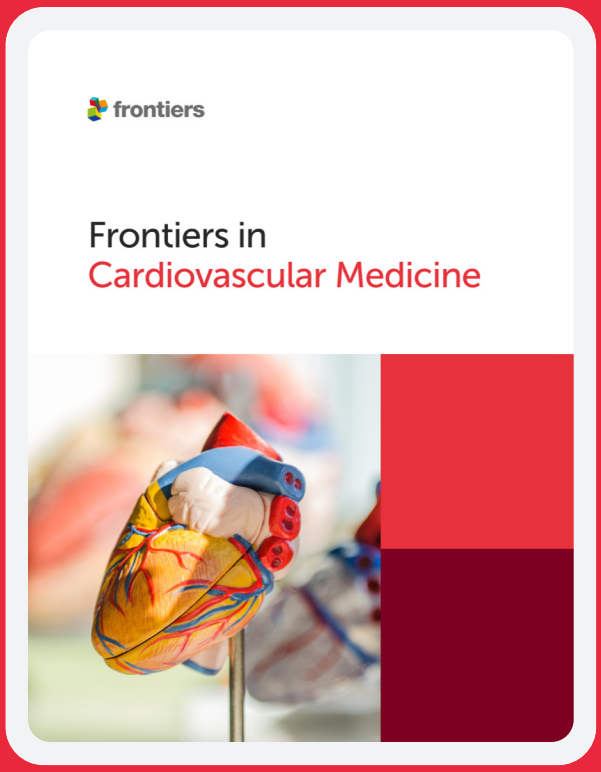

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