

Reclassification of adolescent hypertension by ambulatory blood pressure monitoring using adult norms and association with left ventricular hypertrophy

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Abstract

2017 pediatric blood pressure (BP) guidelines applied adult BP norms to define clinic hypertension (HTN) in patients ≥ 13 years. 2014 pediatric ambulatory BP monitor (ABPM) guidelines recommend age- and sex-specific percentile norms for patients < 18 years. The authors evaluated reclassification of HTN when applying adult ABPM norms in patients ≥ 13 years and assessed the association of left ventricular hypertrophy (LVH) with HTN. Charts of patients 13–17 years with ABPM 9/2018–5/2019 were reviewed for sex, age, height, weight, BP medication, ABPM results, and left ventricular mass index (LVMI). American Heart Association 2005 (AHA 2005), AHA 2017 (AHA 2017), and European Society of Hypertension 2018 (ESH 2018) guidelines for adult ABPM were compared with 2014 AHA pediatric norms (pABPM). HTN was defined by each guideline using only ABPM. ABPM and clinic BP were used to classify white coat hypertension (WCH) and masked hypertension (MH). LVH was defined as $LVMI > 51 \text{ g/m}^{2.7}$. 272 patients had adequate ABPM. 124 patients also had echocardiogram. All adult norms resulted in significant reclassification of HTN. LVMI correlated significantly with systolic BP only. The odds of a patient with HTN having LVH was significant using AHA 2005 (OR: 8.75 [2.1, 36.4], $p = .03$) and ESH 2018 (OR: 4.94 [1, 24.3], $p = .002$). Significant reclassification of HTN occurs with all adult norms. HTN is significantly associated with LVH using AHA 2005 and ESH 2018. Applying pediatric norms for ABPM while using adult norms for clinic BP causes confusion. Guideline selection should balance misdiagnosis with over-diagnosis.

1 | INTRODUCTION

The prevalence of hypertension (HTN) in children and adolescents has been on the rise in the last decade.¹ This increased prevalence of HTN has highlighted the need for further research and

guidelines for diagnosis and management. Blood pressure norms in pediatrics are derived from population data for both clinic and ambulatory blood pressures as opposed to adult norms which are based on outcome data. Because the pediatric definition is based on age, sex, and height derived from population data, norms for

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older adolescents often exceed the normal threshold for adults. In 2017, the American Academy of Pediatrics (AAP) updated the recommendations published in the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (Fourth Report)² and published Clinical Practice Guidelines (2017 CPG).³ One of the primary changes from the Fourth Report was the 2017 CPG recommending the use of adult norms for all children 13 years and older for the diagnosis of HTN by clinic measurement, rather than their 95th percentile for age, sex, and height. Blood pressure (BP) < 120/80 mm Hg is normal, 120–129/80 mm Hg is elevated BP (previously pre-hypertension), 130–139/80–89 mm Hg is stage I hypertension, and \geq 140/90 mm Hg is stage II hypertension.

Several studies have compared the prevalence of HTN using the Fourth Report vs. the 2017 CPG definitions for clinic BP. In a large, school-based study by Bell et al, the prevalence of elevated BP increased by 1.5%. The prevalence of confirmed stage 1 HTN decreased by 1.7% overall but was dependent on the age of the patient. This resulted in more young children with elevated BP (vs. normal BP) and more adolescents with elevated BP (vs. HTN).⁴ In a large, international study, Yang et al found the prevalence of elevated BP decreased (14.9% vs. 8.6%), while the prevalence of HTN increased (16% vs. 7%) when using the 2017 CPG compared with the Fourth Report. Boys, adolescents, and overweight/obese individuals were more likely to be reclassified upward.⁵ The results were similar in a study among Chinese children by Luo et al⁶ Antolini et al reported a 12% increase in the prevalence of elevated BP or HTN (BP \geq 90th) when using the 2017 CPG. The use of the 2017 CPG led to reclassification in 30% of those \geq 13 years old (15% reclassified upward and 15% reclassified downward).⁷

Additionally, studies have evaluated the association of end-organ damage in hypertensive patients defined by the Fourth Report, but there are limited data assessing how the association changes when defining HTN by the 2017 CPG clinic BP measurements.⁸ Children reclassified upward with 2017 CPG (vs. Fourth Report) were 2.18 (1.23–3.88) more likely to have left ventricular hypertrophy (LVH) in adulthood.⁹ Antolini et al found similar results in the association of LVH with HTN for both the Fourth Report (OR: 1.95 [1.4–2.72], $p < .0001$) and 2017 CPG (OR: 2.08 [1.49–2.9], $p < .0001$).⁷

The 2017 CPG also recommend the use of ambulatory blood pressure monitor (ABPM) for the diagnosis of HTN. The guidelines for defining HTN based on clinic BP measurements now align with adult parameters for children and adolescents 13 years and older. However, when defining HTN based on ABPM, the pediatric guidelines (pABPM 2014) continue to recommend using sex and age- or height-based thresholds regardless of age, height, or threshold.¹⁰ Using these thresholds, the definition of HTN in some children and adolescents is higher than the thresholds for adult guidelines. The age/height at which this occurs differs depending on the adult guideline used, but tends to occur in older, taller males. In the past 5 years, there have been three different guidelines available for adults. The American Heart Association

Guidelines from 2017 (AHA 2017) for HTN in adults¹¹ changed the threshold for defining HTN by ABPM from their previous 2005 guidelines (AHA 2005).¹² The European Society of Hypertension 2018 (ESH 2018) guidelines use yet a different threshold for defining HTN.¹³

While reclassification of clinic BP has been evaluated using the new adult thresholds, there is scarce literature on the application of adult ABPM guidelines to define HTN in adolescents 13 years and older who exceed height- or age-based threshold. Whether reclassification of HTN in adolescents based on AHA 2005, AHA 2017, or ESH 2018 norms changes the association with target organ damage as assessed by LVH is not known. We sought to evaluate the reclassification of HTN by ABPM alone and in combination with clinic BP in adolescents 13 years and older based on AHA and ESH guidelines. Furthermore, we investigated the association of LVH with HTN defined by all four ABPM guidelines.

2 | METHODS

2.1 | Study participants

This was a retrospective study of all patients 13–17 years old who wore an ABPM between 9/2018 and 5/2019 in the Renal, Cardiology, and Multi-Disciplinary Hypertension Clinics at a large pediatric hospital-based outpatient center. All patients with complete ABPM data were included for the analysis of blood pressure classification (HTN vs. no-HTN) based on ABPM alone and the classification of white coat HTN (WCH) vs. no-WCH and masked HTN (MH) vs. no-MH using ABPM and clinic BP. Patients who completed an echocardiogram were also included in an analysis of the association between HTN and LVH (Figure 1). Demographic data were collected from the electronic medical record (EMR) and included age, height, weight, sex, and race/ethnicity. Body mass index (BMI) was calculated. The study was approved by the institutional review board of Baylor College of Medicine.

2.2 | Study procedures

2.2.1 | Blood pressure

Space Lab 90 217 and Space Lab 90 227 monitors were used. ABPMs were placed per clinic protocol, using the proper size cuff on the non-dominant arm. Measurements were obtained every 20 min from 6:00 a.m. to 10:00 p.m. and every 30 min from 10:00 p.m. to 6:00 a.m. Wake and sleep times were defined by patient report, if provided. Otherwise, default sleep times (10:00 p.m.–6:00 a.m.) were utilized for analysis.

Clinic BP and use of antihypertensive medication at the time of ABPM placement were obtained from the EMR. Clinic BP was measured by oscillometric monitors and in some patients by auscultation. When three or more BP measurements were documented, the

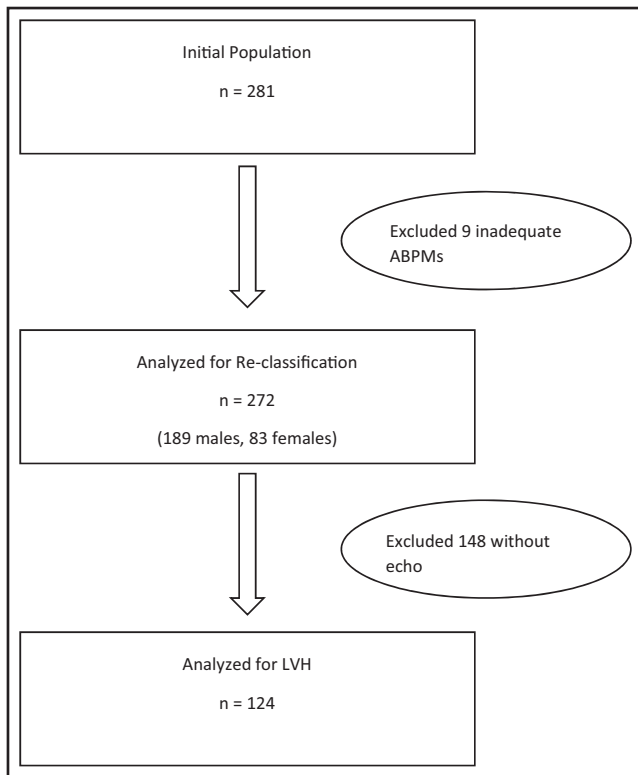


FIGURE 1 Flow diagram of patient selection

average of the last two measurements was collected. If only two measurements were documented, the second measurement was collected, and a single BP measurement was used if it was the only reading documented. Auscultatory measurements were collected preferentially if available. Some readings were taken in the vital sign station upon arrival, and others were repeated later in the visit. Clinic HTN was defined as BP \geq 130/80 mm Hg.

ABPM data were collected from the Sentinel software database and included systolic and diastolic BP mean and load for 24-h, wake, and sleep periods. Adult norms for the definition of HTN based on the AHA 2005, AHA 2017, and ESH 2018 ABPM guidelines were applied to determine BP classification (HTN vs. no-HTN). The thresholds used by AHA 2005 are 135/85 mm Hg for 24 h, 140/90 mm Hg for daytime, and 125/75 mm Hg for nighttime. AHA 2017 uses 125/75 mm Hg, 130/80 mm Hg, and 110/65 mm Hg, respectively, and ESH 2018 utilizes 130/80 mm Hg, 135/85 mm Hg, and 120/70 mm Hg, respectively. HTN using adult norms was defined as a systolic or diastolic 24-h, wake, or sleep BP mean greater than or equal to the respective adult threshold.

The classification of BP status by adult norms was compared with the classification by the pABPM 2014 norms. HTN was defined by pABPM 2014 as systolic or diastolic 24-h, wake, or sleep BP mean \geq 95th percentile for age and sex, and load \geq 25%. Normative data for 95th percentile by sex and age were used for derivation of Z scores.¹⁴

WCH and MH were defined by combining clinic BP with ABPM data according to each of the guidelines (AHA 2005, AHA 2017, and ESH 2018).

TABLE 1 Demographics (N = 272)

Variables	N (%)
Sex	
Females	83 (31)
Males	189 (69)
Race	
Asian	16 (5.8)
African American	49 (18)
Caucasian	186 (68.4)
Other	1 (0.4)
Unknown	20 (7.4)
Ethnicity	
Non-Hispanic	113 (41.5)
Hispanic	140 (51.5)
Unknown	19 (7)
	Mean
	value \pm SD
	(range)
Age (years)	15.7 \pm 1.37 (13.03–17.99)
BMI (kg/m ²)	30.5 \pm 8.92 (12.97–68.33)

2.2.2 | LVH

Left ventricular mass index (LVMI) measurements were obtained from echocardiogram reports in the EMR. LVH was defined according to the 2017 CPG as LVMI $>$ 51 g/m^{2.73}.

2.3 | Statistical analysis

Statistical analysis was performed with Stata[®] software (version 15 Stata Corp, College Station, TX). Continuous variables are expressed as mean \pm standard deviation. Frequencies are presented as percentages. Misclassification between pediatric norms and adult norms with regard to both classifications of ABPM HTN and for WCH and MH was done by McNemar's test. The associations between LVH and HTN by pediatric and adult norms were assessed with logistical regression and controlled for age, sex, ethnicity, and BMI. *p* value $<$.05 was considered significant.

3 | RESULTS

A total of 272 patients (189 males and 83 females) were included in the analysis for reclassification of HTN. Of those, 124 patients also had LVMI data and were analysed for LVH. The mean age was 15.7 years (SD: 1.37). Other demographic data are displayed in Table 1. In the table, the population is primarily Caucasian, but the

table does not differentiate from Hispanic and non-Hispanic whites. With this differentiation, 49% of the population is Hispanic; 19%, non-Hispanic white; and 18%, black. The ethnic/racial breakdown is reflective of the demographics for the city where the hospital is located. Majority of patients were either obese (122 patients, 45%) or overweight (78 patients, 29%).

The prevalence of HTN, WCH, and MH differed by guideline utilized (Figure 2). AHA 2017 revealed the highest percentage of HTN and the least percentage of WCH, while AHA 2005 identified the most patients with WCH and the least HTN patients.

3.1 | Reclassification of hypertension

All adult norms resulted in significant differences in the reclassification of HTN based on ABPM alone. As expected, the adult norms with the highest thresholds (AHA 2005) reclassified more patients from HTN to no-HTN, while the adult norms with the lowest thresholds (AHA 2017) reclassified more patients from no-HTN to HTN (Table 2). The patients reclassified from HTN to no-HTN were younger (median age: 14.7–15.5 vs. 15.9–16.9) and more likely to be females.

A significant number of patients were also reclassified from no-HTN to HTN (16%) using the AHA 2017 guidelines. These were nearly all tall (median height 172 vs. 168 cm) males.

3.2 | Reclassification of white coat and masked hypertension

A similar pattern was observed with WCH vs. no-WCH and MH vs. no-MH as well. The adult norms with the highest thresholds (AHA 2005) were associated with an increased percentage of patients reclassified from no-WCH (a.k.a. HTN) to WCH compared with the other thresholds. While the adult norms with the lowest thresholds

(AHA, 2017) were associated with an increased percentage of patients reclassified from WCH to no-WCH (a.k.a. HTN) (Table 2).

The adult norms with the highest thresholds (AHA 2005) were associated with an increased percentage of patients reclassified from MH to no-MH (a.k.a. normotensive) compared with the other thresholds. Alternatively, the adult norms with the lowest thresholds (AHA, 2017) were associated with an increased percentage of patients reclassified from no-MH to MH (Table 2). Only a small percentage of patients were reclassified from MH to no-MH or no-MH to MH when comparing the pediatric norms to any of the adult norms.

3.3 | Left ventricular hypertrophy

LVMI correlated significantly with systolic BP (24 h, awake, asleep mean, and load) but not diastolic BP, independent of sex (Figure 3). The odds of a patient with HTN having LVH was significant only when defined by AHA 2005 and ESH 2018 norms (OR: 8.75 [2.1, 36.4], $p = .03$, and OR: 4.94 [1, 24.3], $p = .002$, respectively) (Figure 4). This correlation was independent of age, sex, ethnicity, or BMI.

4 | DISCUSSION

We evaluated the reclassification of HTN defined by ABPM alone and by the combination of clinic BP and ABPM to further classify WCH and MH when applying 3 different adult ABPM norms compared with pediatric norms in patients 13 years and older. The AHA 2005 guidelines use the highest thresholds, and the AHA 2017 guidelines utilize the lowest thresholds. Additionally, we assessed the association between LVH and HTN when applying the various norms. This association with various ABPM norms has not previously been reported in the literature. Clinically, applying pediatric norms for ABPM while using adult norms for clinic BP

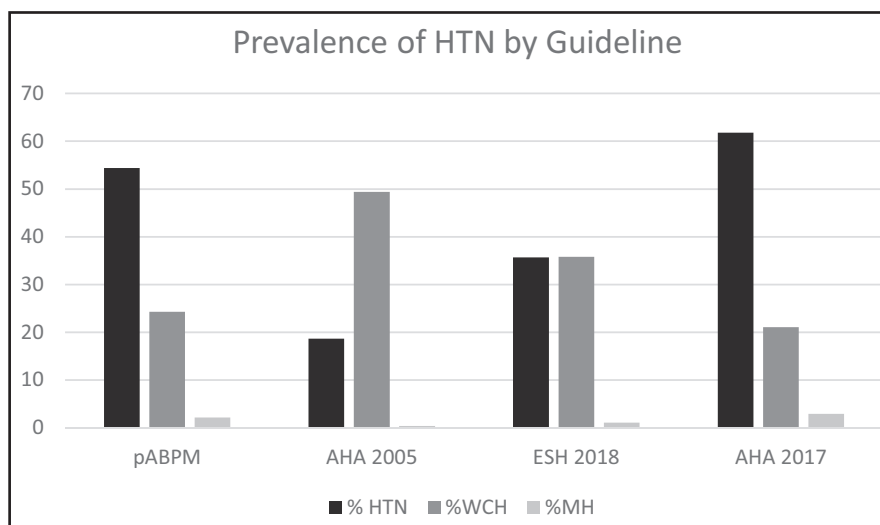


FIGURE 2 Prevalence of HTN by guideline

TABLE 2 Reclassification of HTN, WCH, and MH by adult norms

		AHA 2005		ESH 2018		AHA 2017	
		No-HTN	HTN	No-HTN	HTN	No-HTN	HTN
pABPM 2014	No-HTN	44.9%	0.7%	43.4%	2.2%	30.1%	15.5%
	HTN	36.4%	18.0%	20.9%	33.5%	8.1%	46.3%
	<i>p</i> by χ^2	<0.001		<0.001		<0.001	
		No-WCH	WCH	No-WCH	WCH	No-WCH	WCH
	No-WCH	50.7%	25.0%	63.2%	12.5%	70.9%	4.8%
	WCH	0%	24.3%	1.1%	23.2%	8.1%	16.2%
	<i>p</i> by χ^2	<0.001		<0.001		<0.001	
		No-MH	MH	No-MH	MH	No-MH	MH
	No-MH	97.8%	0%	97.8%	0%	96.7%	1.1%
	MH	1.8%	0.4%	1.1%	1.1%	0.4%	1.8%
	<i>p</i> by χ^2	<.05		<0.001		<0.001	

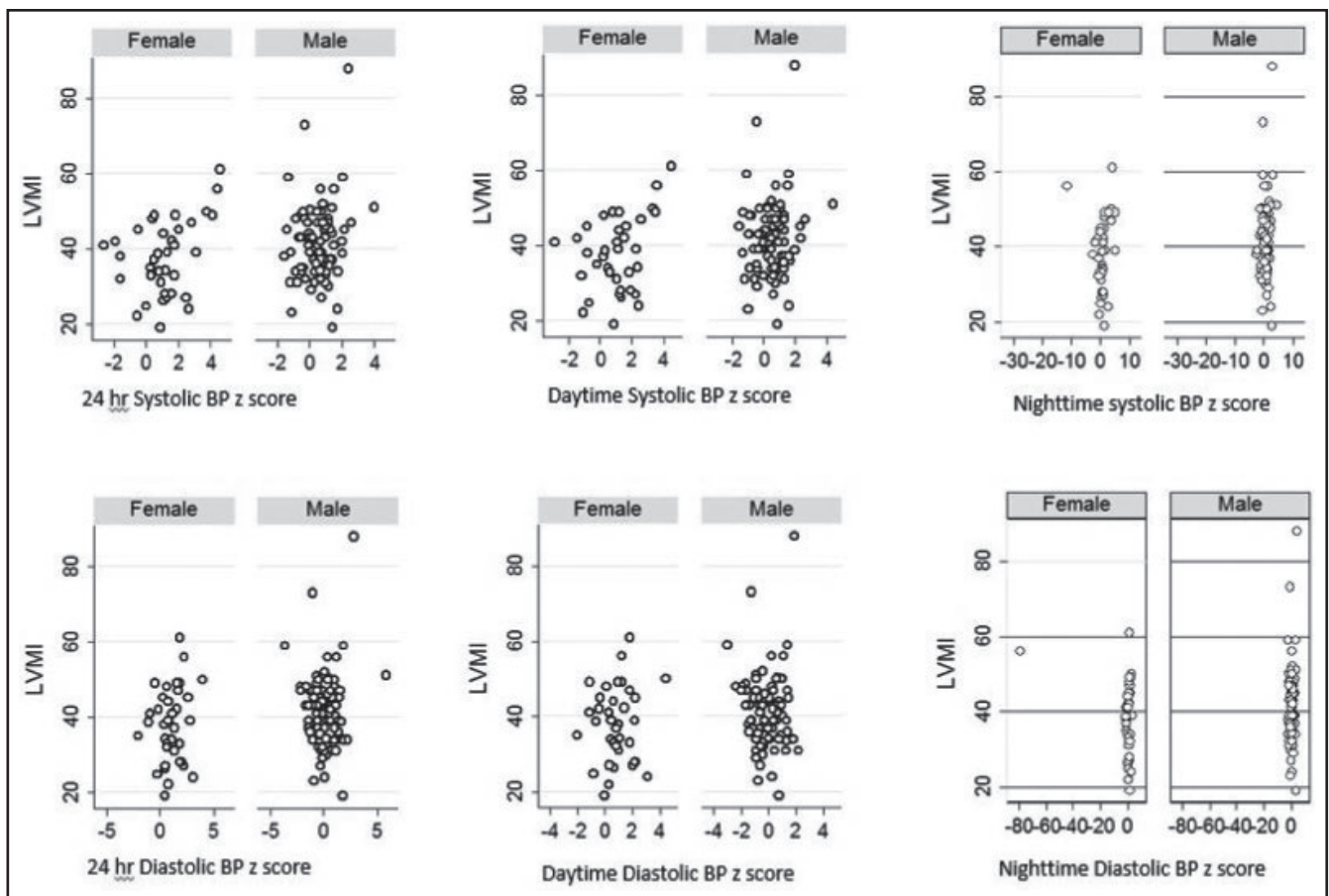


FIGURE 3 Correlation of LVMI and ABPM z-score by sex

leads to confusion and raises the question of similarly applying adult norms for ABPM in children 13 years and older. Of note, the 2016 ESH guidelines for the management of BP in children recommend the use of 95th percentile unless it exceeds the accepted adult thresholds.¹⁵

We found significant misclassification or rather reclassification (since pediatric standards are not necessarily evidence-based)

regardless of which adult norms were applied. This is similar to previous studies^{16,17} wherein applying different norms resulted in significant reclassification. Perhaps the most clinically significant reclassification is of those patients reclassified from no-HTN to HTN as these are the patients who are missed when using the current pediatric norms. The AHA 2017 norms identified the largest proportion of those patients when compared to AHA 2005 or ESH 2018.

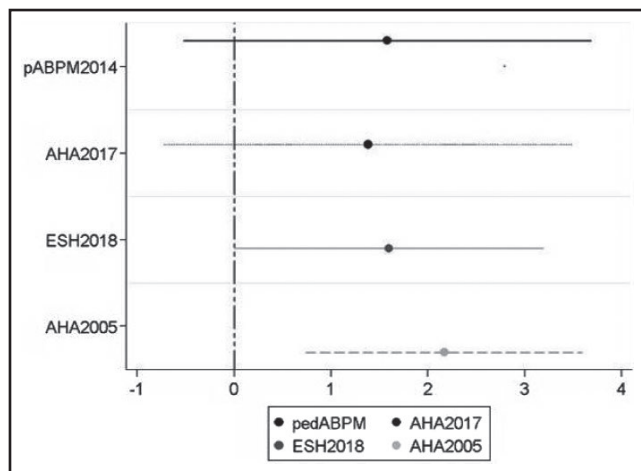


FIGURE 4 β -coefficient plot of LVH association with HTN

However, this could also lead to over-diagnosis without evidence to support the need for this reclassification.

A similar pattern was observed with WCH vs. no-WCH and MH vs. no-MH. In this case, those patients reclassified from WCH to no-WCH (a.k.a HTN) are the biggest clinical concern. The AHA 2017 guidelines had the highest percentage of these patients. Alternatively, the largest proportion of reclassification overall occurred from no-WCH to WCH when the 2005 AHA guidelines were applied. The same pattern was seen for MH. The overall reclassification with all adult norms was significant, but the changes in proportions were smaller for MH. Again, the AHA 2017 norms resulted in the largest proportion of change from no-MH to MH, while the AHA 2005 norms had the largest change in proportion from MH to no-MH. All scenarios exemplify the need for careful balance in clinical practice between misdiagnosis and over-diagnosis.

Previous studies have evaluated the impact of reclassification of clinic BP when applying various normative data to a pediatric population,^{5,6} but few have evaluated the impact on ABPM classification.^{16,17} Two previous studies evaluated the impact of ABPM reclassification using pediatric norms and ESH norms. Sharma et al only included 24-h mean and load to diagnose HTN comparing the use of pABPM 2014 norms and pediatric ESH norms of 95th percentile or >130/80 mm Hg (adult threshold) when the 95th percentile exceeds 130/80 mm Hg.¹⁷ They found the age where participants required the adult threshold were 13 years. When using AAP CPG to define clinic BP in patients 13 years and older, only 81% of the cohort was classified the same using the two different ABPM guidelines. Unlike our study, there was no difference in the classification of WCH between the two reference guidelines in patients 13 years or older. However, there were 5% more participants identified with MH when applying the ESH norms. Although the number of participants for this study was similar to ours, the percentage of participants 13 years and older was only 91 (57%), and of those, only 25 required the use of adult thresholds. This smaller sample size and limited application of the adult thresholds likely accounts for the differences in results.

A similar study by Lurbe et al compared changes in BP classification using AAP/AHA standards vs. ESH standards: AAP CPG 2017

vs. ESH norms for clinic BP and AHA vs. ESH ABPM guidelines for ABPM norms.¹⁶ Again, both guidelines use 95th percentile to define ambulatory HTN, but ESH 2016 guidelines use 135/85 mm Hg when the 95th percentile exceeds 135/85 mm Hg. They also found a significant difference in the prevalence of WCH and MH, but no significant difference in the classification of sustained hypertension or normotension. The AAP/AHA guidelines classified a higher percentage with WCH than the ESH guidelines, and the ESH guidelines classified more participants with MH but with less difference in the classification of MH. Masked HTN is prevalent in children with CKD,¹⁸ and one study evaluating a CKD adolescent cohort found a similar pattern to our study for reclassification of HTN by ABPM alone when comparing the pABPM 2014 guidelines to AHA 2005 and AHA 2017 norms. The AHA 2017 norms classified the highest percentage with HTN (44%), followed by pABPM 2014 (27%), and AHA 2005 (16%) [Lee, J.T et al Discordances Between Pediatric and Adult Thresholds in the Diagnosis of Ambulatory Hypertension in Adolescents with CKD. ASN Kidney Week; November 7–10, 2019, Washington DC].

In an effort to address the balance between over-diagnosis and misdiagnosis, we evaluated LVH and found LVH was significantly associated with HTN when defined by AHA 2005 and ESH 2018 norms. Patients with HTN defined by the AHA 2005 norms had the highest odds of having LVH. Similarly in the adolescent CKD cohort study, when comparing HTN defined by pABPM, AHA 2005, and AHA 2017 norms, the AHA 2005 norms had the highest specificity for LVH though the lowest sensitivity [Lee, J.T et al Discordances Between Pediatric and Adult Thresholds in the Diagnosis of Ambulatory Hypertension in Adolescents with CKD. ASN Kidney Week; November 7–10, 2019, Washington DC]. Our study is in agreement with the above study, but potentially more generalizable since we had very few secondary causes of HTN. Both the AHA 2005 and ESH 2018 guidelines provide ABPM norm thresholds higher than the AHA 2017 guidelines (AHA 2005 having the highest) which would suggest less over-diagnosis, but one could argue that the presence of LVH at the time of diagnosis is a late diagnosis.

To our knowledge, this is the first study assessing the association between LVH with HTN as defined by various ABPM norms combined with clinic BP in a general pediatric population. Using pediatric norms (pABPM 2014) as the reference standard, we not only demonstrate significant reclassification with all three adult thresholds, but we identified which norms resulted in an association between LVH and HTN. However, the retrospective nature and sample size of our study are a limitation. Ideally, larger and potentially prospective studies are needed to provide true evidence-based normative data.

Though both ESH 2018 adult norms and AHA 2005 adult norms had significant association with LVH, the argument could be made for using the AHA 2017 norms to potentially diagnose HTN before the development of LVH. In summary, similar to the use of adult norms for clinic BP in children 13 years and older, adult ABPM norms for the same population would be ideal. However, careful consideration has to be given for using the most appropriate guidelines, since reclassification would occur with regard to HTN and association of LVH in each of these adult ABPM norms.

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CONFLICT OF INTEREST

Jessica Fallon Campbell, Shweta Shah, and Alisa Acosta: None. Poyyapakkam Srivaths attended Advisor Board Meeting for Reata Pharma.

AUTHOR CONTRIBUTIONS

All authors conceived the idea and planned the research project. All authors participated in the collection of data. Poyyapakkam Srivaths analysed and interpreted the data. All authors discussed the interpretation of data. All authors were actively involved in drafting and revising the manuscript, and all authors approved the final submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. The current IRB for the study does not support sharing of the data since available data is from a single institution and not a public entity.

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