

# Blood Pressure and Glomerular Filtration Rate in Youth With Tuberous Sclerosis Complex

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## Research Article

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# Abstract

## Background

Renal involvement is very common in tuberous sclerosis complex (TSC) and is characterised by the development of angiomyolipoma and cysts. The aims of the present study were to assess kidney function and clinical features of renal involvement in TSC, including kidney function, and blood pressure (BP) levels in children, adolescents and young adults.

## Methods

Non-selected patients with a definite diagnosis of TSC attending the paediatric neurology outpatient department of a tertiary hospital were included in a cross-sectional study. All participants had a renal imaging study within 6 months of ambulatory blood pressure (BP) and glomerular filtration rate (GFR) assessment. Data on demographics, history, genotype, kidney function at diagnosis and last imaging were collected.

## Results

The median age of the patients was 15 years (IQR range 9 to 18). 23.5% of the participants had ambulatory BP hypertension. Systolic BP levels correlated significantly with  $GFR_{DTPA}$  values despite the absence of hyperfiltration. Greater increase in GFR from initial TSC diagnosis till the age of the assessment, resulted in higher GFR levels in childhood and adolescence in those that developed hypertension and possibly in those with angiomyolipoma or cysts. All patients with ambulatory BP hypertension had angiomyolipomas or cysts on renal imaging studies.

## Conclusions

Hypertension may present with increased frequency in young patients with kidney disease associated with TSC. Routine ambulatory BP measurement could be part of the annual clinical assessment in patients with TSC.

## What Is Known

- Nearly half of the patients with TSC have a premature decline in their renal function in their fifth decade of life
- Hypertension and hyperfiltration have been proposed as modifiable factors of progression of renal decline

## What is new:

- Hypertension is prevalent in youth with tuberous sclerosis complex
- SBP levels have a positive relation with GFR levels within the normal range of  $GFR_{DTPA}$  values

## Introduction

Tuberous sclerosis complex (TSC) is a rare multisystemic genetic disorder inherited in an autosomal dominant manner. Its incidence has been estimated to be 1 per 5,800 live births and approximately 2 million people are affected worldwide [1, 2]. TSC is caused by mutations in one of the two tumor suppressor genes, TSC1 (9p34.13) and TSC2 (16p13.3), which encode two proteins, hamartin and tuberin respectively [3–5]. These two proteins form a heterodimeric complex that inhibits the mechanistic target of rapamycin (mTOR) signaling pathway. Pathogenic mutations to the aforementioned genes disrupt the mTOR cascade leading to relatively unregulated cell growth and proliferation. The hallmark of the disease is the formation of benign tumors (hamartomas) in various organs, such as brain, kidneys, lungs, heart, eyes and skin [6].

Renal involvement is very common in patients with TSC after neurological manifestations and TSC-associated neuropsychiatric disorders. Its importance is highlighted by studies demonstrating that renal disease is a major cause of mortality in the TSC population [7–9]. Angiomyolipoma (AML) is the most prevalent renal lesion in TSC followed by cystic disease [10]. According to Bissler et al., around 40% of patients with TSC have a premature decline in their renal function with an estimated glomerular filtration rate (eGFR) < 60ml/min in their fifth decade of life compared to only 3% of the general population [11]. Besides AMLs and renal cysts, hypertension, proteinuria and hyperfiltration have been recently proposed as modifiable factors of progression of renal decline and subsequently preventive treatment targets [12]. However, to our knowledge, the prevalence of hypertension by ambulatory blood pressure (BP) monitoring and assessment of BP associations with measured GFR or imaging findings, that could guide early management, has not been investigated in young patients with TSC. The aims of the present study were to assess kidney function and clinical features of renal involvement in TSC, including GFR, albuminuria, and BP levels in children, adolescents and young adults.

## Methods

### Population

In this study we included children, adolescents, and young adults with a confirmed TSC diagnosis who were followed up at the neurology outpatient clinic of the 1st Department of Pediatrics. Inclusion criteria in the study were: a. definite clinical or genetic diagnosis of TSC, b. age > 5 years and age < 24 years, c. kidney imaging study within 6 months of GFR and BP assessment, and d. consent to participate in the study. From the historic TSC cohort, after excluding older patients transferred to adult care and 3 patients that did not attend their annual follow up visit, 20 patients fulfilled the study criteria.

Informed consent to participate in the study was obtained by children's parents or patients themselves if older than 12 years. The human research protocol was conducted according to the Helsinki declaration for human clinical studies and approved by the institutional review board.

## Demographic, clinical and imaging data collection

Demographics, family history, genotype, presenting features, organ involvement, serum creatinine at diagnosis, and last imaging findings were recorded from patient files. The presence of AMLs and cysts, with the number, size, and location were recorded from last imaging study either magnetic resonance imaging (MRI), or ultrasound (US), or computed tomography (CT). The diameter of the largest AML and cyst was also documented for each kidney.

Microscopic urine examination, and albuminuria were assessed on a morning urine spot. Albuminuria was also measured on a 24-h collection and was defined as albumin excretion rate > 30 mg/24 hours or albumin to creatine ratio > 30 mg/g [13].

## Glomerular Filtration Rate

GFR was measured by  $^{99m}\text{Tc}$ -DTPA scan ( $\text{GFR}_{\text{DTPA}}$ ) in all patients [14, 15]. A single intravenous dose of  $^{99m}\text{Tc}$ -DTPA (diethylenetriaminepentaacetic acid) was administered to each patient according to the age and weight of the patient. Radioactivity was recorded by a multi-function well counter after selection of the adequate energy peak and window, each plasma sample and standard vial being counted twice. Background activity was also measured in the beginning and at the end of the counting. All measurements were corrected for  $^{99m}\text{Tc}$  decay, taking into account the delay of time between the successive measurements in the well counter. The decrease in  $^{99m}\text{Tc}$ -DTPA in blood plasma with time is given by the injected dose divided by the area under the curve; the latter being best described by a biexponential function. Haycock method has been used for body surface estimation from height and weight. GFR was normalized to body surface area and its values were expressed in ml/min/1.73 m<sup>2</sup>.

GFR was also estimated by using 4 different equations, the original Schwartz formula ( $\text{GFR}_{\text{Schwartz}}$ ), the Creatinine-based Bedside Schwartz equation ( $\text{GFR}_{\text{Bedside Schwartz}}$ ), the Cystatin-C based equation ( $\text{GFR}_{\text{Cystatin-C}}$ ), and the Creatinine-Cystatin C-based CKiD equation ( $\text{GFR}_{\text{CKiD}}$ ), at the day of  $^{99m}\text{Tc}$ -DTPA scan [16–18]. Serum creatinine was measured using the Jaffe-based creatinine-picrate forming in an alkaline medium [19]. The measurement was performed using the Architect c16000 automated analyser (Abbott Diagnostics Inc, Park City, IL, USA). Cystatin-C was measured by particle-enhanced nephelometric immunoassay on BN ProSpec® Behring nephelometer system [20].  $\Delta\text{GFR}_{\text{Schwartz}}$  was also defined as the difference between  $\text{GFR}_{\text{Schwartz}}$  at last visit and initial  $\text{GFR}_{\text{Schwartz}}$ . Chronic kidney disease (CKD) stage was classified according to the KDIGO guidelines [13]. Hyperfiltration was defined as  $\text{GFR} \geq 140$  ml/min/1.73m<sup>2</sup>[21].

## Blood pressure measurements

Office BP measurement was performed by a trained physician. Appropriate cuff size was used, and BP was measured on the right arm to the nearest 1 mmHg with the child or adolescent quiet, seated with the back supported, and feet uncrossed on the floor after a 5-min rest. Office hypertension was defined in children and adolescents younger than 16 years old as systolic BP (SBP) and/or diastolic BP (DBP)  $\geq$  95th percentile for sex, age and height. For adolescents  $\geq$  16 years old the cut-off for office hypertension was SBP/DBP  $\geq$  140/90 mmHg [22].

The patients underwent 24h ambulatory blood pressure monitoring (ABPM) using the Mobil-O-Graph 24h PWA Monitor (IEM GmbH, Stolberg, Germany). They were instructed to rest or sleep between midnight and 06:00 (night-time) and to maintain their usual activities between 08:00 and 22:00 (daytime). BP readings were obtained every 15 min during daytime and every 20 minutes during night-time. Fitting the monitor, reading and analysing the ambulatory BP data has been previously described [23–25]. ABPM sessions with 75% valid BP measurements were included in the study [26]. Three patients with cognitive impairment and autism did not tolerate ABPM. Ambulatory BP hypertension was defined as 24h and/or daytime and/or night-time BP greater or equal to the 95th ambulatory BP percentile according to sex and height in study participants  $<$  16 years, or the adult ambulatory BP limits in adolescents  $\geq$  16 years [22].

## Pulse wave analysis

Central SBP (cSBP) and pulse wave velocity (PWV) were obtained by Mobil-O-Graph 24h PWA monitor using the ARCSolver algorithm, which reconstructs the central pulse wave by applying a transfer function [27]. In children and adolescent's estimation of cSBP using a Mobil-O-Graph device showed good accuracy compared with simultaneous invasive recordings in children and adolescents (age range 1–18 years) who underwent a cardiac catheterization [28]. Furthermore, reference values for cSBP and PWV are available for the children and adolescents using the Mobil-O-Graph device [29].

## Statistical analysis

The IBM SPSS 24.0 (SPSS Inc, Chicago, Illinois, USA) statistical package was used to analyze the data. Standard descriptive statistics, t-test or non-parametric methods (Chi-Square, Mann-Whitney tests) were used as appropriate for the comparison between the groups. Regression analysis and Bland-Altman plots were used for the comparison of the different GFR equations with  $GFR_{DTPA}$ . Regression analysis was also used to examine associations between GFR and BP values. Estimated marginal means (EMMs) after Bonferroni adjustment for multiple comparisons were used to assess for differences on final GFR and deltaGFR levels between patients' groups by BP levels or presence of AML or cysts. A  $p$  value  $<$  0.05 was considered statistically significant.

## Results

### General characteristics of the cohort

Median age at presentation was 36 (IQR 7–66) months. At the last visit median age was 15 (IQR 9–18) years. Mean duration of follow up was  $10.1 \pm 5.58$  years. The demographic and clinical characteristics of

the cohort are presented in Table 1.

Table 1  
Patient characteristics

<b>Variable</b>	<b>Median (IQR) or n (%)</b> <b>(n = 20)</b>
<b>Median age at presentation</b>	36 (IQR 7–66) months
<b>Male/female</b>	12/8 (60%/40%)
<b>Median age at study visit</b>	15 (IQR 9–18) years
<b>Genetic testing</b>	3 (15%)
Mutations	TSC1 (del exons 19–23) TSC2 exon 41 (c.5227C > T p.Arg1743Trp) TSC2 (del exons 1–29)
<b>Prenatal diagnosis</b>	None
<b>Family history</b>	8 (40%)
<b>Presenting symptom</b>	Neurological 17 (85%) Renal 1 (5%) Asymptomatic 2 (10%)
<b>Kidney imaging modality (%)</b>	MRI 16 (80%) US 4 (20%)
<b>Angiomyolipoma</b>	9 (45%)
Multiple	9 (100%)
Bilateral	9 (100%)
Size > 3mm	6
<b>Cysts</b>	4 (20%)
Multiple	2 (50%)
Bilateral	1 (25%)
Size > 3mm	2 (50%)
<b>Treatment</b>	
Everolimus	8 (40%), 2 patients are treated for angiomyolipoma
Anti-epileptic drugs	10 (50%)
<i>MRI: magnetic resonance imaging, US: ultrasound, IQR: interquartile range</i>	

# Kidney Function

Mean  $GFR_{Schwartz}$  at presentation was  $101.81 \pm 14.02$  ml/min/1.73m<sup>2</sup>. At end of follow up mean  $GFR_{Schwartz}$  was  $125.89 \pm 25.78$  ml/min/1.73m<sup>2</sup> resulting in mean  $\Delta GFR_{Schwartz}$  of  $23.90 \pm 30.91$  ml/min/1.73m<sup>2</sup>. At last visit mean  $GFR_{DTPA}$  was  $98.85 \pm 14.37$  ml/min/1.73m<sup>2</sup>.  $GFR_{Bedside\ Schwartz}$  and  $GFR_{CKiD}$  equations provided equivalent results to  $GFR_{DTPA}$  values (Table 2).

Table 2  
Comparison of GFR equations with  $GFR_{DTPA}$

Equation	Mean $\pm$ SD	Mean <sub>diff</sub> $\pm$ SD <sub>diff</sub>	Limits of agreement	ICC
$GFR_{Schwartz}$	$125.89 \pm 25.78$	$-27.04 \pm 23.44^*$	(-91.88,18.9)	-0.56*
$GFR_{Bedside\ Schwartz}$	$92.85 \pm 16.25$	$6 \pm 19.15$	(31.53,43.53)	-0.12
$GFR_{Cystatin-C}$	$108.85 \pm 21.37$	$-10 \pm 19.06^*$	(-47.35,27.35)	-0.42
$GFR_{CKiD}$	$95.35 \pm 14.62$	$3.5 \pm 14.63$	(25.17,32.13)	-0.02
<i>SD: standard deviation, ICC: intercorrelation coefficient</i>				
<i>*p &lt; 0.05</i>				

There were no patients with  $GFR < 60$  ml/min/1.73m<sup>2</sup> or albuminuria. However, four patients presented with stage 2 CKD at the end of follow up. No patient presented with hyperfiltration.

$GFR$  levels did not differ between patients by presence of AML, cysts, or hypertension.  $\Delta GFR_{Schwartz}$  was higher in those with ambulatory BP hypertension, but the difference did not reach significance. However,  $\Delta GFR_{Schwartz}$  adjusted for age at presentation, current age and sex, was statistically significant higher in those with ambulatory BP hypertension (EMMs 43.90 95%CI 29.06–58.75 versus 16.48, 95%CI 8.99–24.01 in normotensives,  $p < 0.005$ ). Moreover,  $\Delta GFR_{Schwartz}$  adjusted for age at presentation, current age and sex, was higher in those with AML or cysts but did not reach significance (EMMs 26.57 95% CI 17.51–35.63 versus 15.05 95%CI 5.23–24.88 in normal imaging,  $p = 0.08$ ).

## Blood Pressure

BP z scores levels did not differ significantly between patients with AML or cysts and those with no findings on kidney imaging (Table 3). Five patients (26.5%) had office hypertension. AML or cysts was found in 3 out of 5 children (60%) with office hypertension (Fig. 1a). Amongst 17 patients who underwent ABPM, 4 (23.5%) patients had hypertension. All patients with ambulatory BP hypertension had AML or cysts (Fig. 1b). They were all male, half of them had a positive family history of tuberous sclerosis, 3 had multiple bilateral AMLs with maximum size  $\geq 10$ mm (Table 4). None of the hypertensive patients

identified was receiving antihypertensive therapy, while 3 were receiving treatments with everolimus (Table 4). Finally, there was no difference in height adjusted z scores of PWV and cSBP among those with with AML or cysts and those with no findings on kidney imaging.

Table 3  
Office and ABPM parameters

Variable	Normal kidney imaging (n = 10)	Angiomyolipoma or cyst (n = 10)
Office SBP (mmHg)	104.00 ± 9.12	118.50 ± 21.22*
Office DBP (mmHg)	63.67 ± 14.15	69.80 ± 11.51
Office SBP z score	-0.06 ± 1.22	0.98 ± 1.59
Office DBP z score	-0.94 ± 2.67	0.18 ± 2.75
24h SBP (mmHg)	107.88 ± 8.39	118.67 ± 10.77*
24h DBP (mmHg)	63.38 ± 3.66	69.22 ± 9.02
24h MAP (mmHg)	83.88 ± 5.11	91.78 ± 9.15*
24h SBP z score	-0.43 ± 1.15	0.29 ± 1.04
24h DBP z score	-0.68 ± .74	0.13 ± 1.85
24h MAP z score	0.57 ± .91	1.46 ± 1.30
Daytime SBP (mmHg)	110.00 ± 9.59	119.89 ± 11.06*
Daytime DBP (mmHg)	64.75 ± 3.80	70.00 ± 9.42
Daytime MAP (mmHg)	85.63 ± 5.93	91.00 ± 11.94
Daytime SBP z score	-0.77 ± 1.21	-0.25 ± 1.14
Daytime DBP z score	-1.31 ± .68	-0.49 ± 1.50
Daytime MAP z score	0.03 ± .91	0.48 ± 1.63
Night-time SBP (mmHg)	101.86 ± 8.63	115.33 ± 8.50*
Night-time DBP mmHg)	56.14 ± 3.44	66.50 ± 4.51
Night-time MAP (mmHg)	77.29 ± 5.71	89.17 ± 5.71*
Night-time SBP z score	0.15 ± 1.18	1.17 ± .81
Night-time DBP z score	0.13 ± .58	1.73 ± .70
Night-time MAP z score	1.05 ± .92	3.09 ± 1.30

*ABPM: ambulatory blood pressure monitoring, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, cSBP: central systolic blood pressure, PWV: pulse wave velocity*

\**p* < 0.05

Variable	Normal kidney imaging (n = 10)	Angiomyolipoma or cyst (n = 10)
24h cSBP (mmHg)	107.13 ± 9.63	117.44 ± 14.46
24h cSBP z score	1.81 ± 1.46	2.05 ± 1.39
24h PWV (m/sec)	4.42 ± .24	4.83 ± .43*
24h PWV z score	-0.27 ± 1.23	0.11 ± 1.01
<i>ABPM: ambulatory blood pressure monitoring, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, cSBP: central systolic blood pressure, PWV: pulse wave velocity</i>		
* <i>p</i> < 0.05		

Table 4  
Characteristics of patients with ambulatory BP hypertension.

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
Age (y)	17	18	22	16
Sex	Male	Male	Male	Male
Genetic testing	Not performed	TSC2 (c.5227C > T p.Arg1743Trp)	Not performed	TSC1 (del exons 19–23)
Family history	Positive	Negative	Negative	Positive
Presenting symptom	No available data	Neurological	Neurological	Neurological
Kidney imaging modality	MRI	MRI	MRI	MRI
Angiomyolipoma	Bilateral	Bilateral	Bilateral	No
Number	27	8	14	
Max size (mm)	71	14	10	
Cysts	Unilateral	No	No	Unilateral
Number	3			1
Max size (mm)	5			2
Treatment with Everolimus	Yes <sup>+</sup>	Yes*	Yes*	No
<i>*Treatment for subependymal giant cell astrocytoma (SEGA)</i>				
<i><sup>+</sup>Treatment for angiomyolipoma</i>				

GFR<sub>DTPA</sub> values were associated with daytime SBP z score ( $R^2 = 0.42$ ,  $p < 0.005$ ), daytime MAP z score ( $R^2 = 0.38$ ,  $p < 0.05$ ), 24hSBP z score, ( $R^2 = 0.39$ ,  $p < 0.05$ ), 24h MAP z score ( $R^2 = 0.38$ ,  $p < 0.05$ ), 24h cSBP z score ( $R^2 = 0.32$ ,  $p < 0.05$ ), and 24h PWV z score ( $R^2 = 0.29$ ,  $p < 0.05$ ), but not with office BP parameters.

## Discussion

In the present study, we found a 23.5% prevalence of ambulatory BP hypertension and significant positive associations of GFR<sub>DTPA</sub> with SBP values. GFR<sub>DTPA</sub> was used to accurately assess kidney function in this cohort. GFR<sub>Bedside Schwartz</sub> and GFR<sub>CKiD</sub> equations provided equivalent estimation of kidney function, but only GFR<sub>DTPA</sub> presented associations with BP parameters. The present study is to our knowledge the first one that investigated the association of imaging findings and GFR with BP levels using ambulatory BP

monitoring. All children with ambulatory BP hypertension had AML or cysts on kidney imaging. Greater increase in GFR from initial diagnosis to assessment date resulted in higher GFR levels in childhood and adolescence in those that developed hypertension.

Patients with TSC develop renal impairment more frequently and at an earlier age compared to the general population [30]. In the present cohort none of the patients had  $GFR < 60\text{ml}/\text{min}/1.73\text{m}^2$ . Only  $GFR_{DTPA}$  values were found to correlate significantly with ambulatory BP parameters. Hypertension is a known risk factor for progressive decline of renal function. Its incidence in the TSC population with renal disease is higher than in the general population; it increases with age and peaks in the fifth decade of life [10, 31]. The prevalence of hypertension in youth with TSC is poorly investigated. A retrospective study in 35 children and young adults with TSC revealed a 25.7% prevalence of hypertension [32]. A recent multicenter study from Belgium including both pediatric and adult patients reported that 23% (8/35) of patients with TSC < 18 years old had hypertension [12]. A few other reports have highlighted the correlation between TSC-associated renal disease and hypertension in the paediatric age group; the majority of which are *TSC2-PKD1 contiguous gene syndrome* cases [33–37]. In those patients, hypertension is often discovered in infancy and the renal function decline is rapid. The primary cause of hypertension in TSC is the formation of cysts or AML occupying the renal parenchyma. Interestingly, there are a few reports of patients who initially presented with hypertension associated with abdominal pain or distention and eventually diagnosed with TSC [38–40]. Of note, TSC can rarely be associated with vascular malformations leading to renovascular occlusion and refractory hypertension [41]. Finally, a significant number of patients with TSC may be under antiepileptic drug treatment, but there is no solid evidence of any effect of these drugs on BP [42].

It is of interest that statistically significant increase from initial GFR was noted to those with ambulatory hypertension. Despite the greater increase none of these patients presented with hyperfiltration. Renal hyperfiltration is defined as an unexpectedly high GFR ranging between  $130\text{--}140\text{ml}/\text{min}/1.73\text{m}^2$  [21]. There are no current studies investigating the underlying mechanisms of hyperfiltration in the TSC population. However, the encroachment of normal renal parenchyma by growing AML or cysts and the subsequent surgical interventions (i.e., nephrectomy or embolization), which lead to a reduced number of functional nephrons, could result in compensatory hemodynamic changes in response to nephron loss. As a consequence, there will be increased renal blood flow to the remaining normal renal parenchyma potentially leading to intraglomerular hypertension. Another hypothesis is that mTOR pathway overactivity caused by TSC1/TSC2 haploinsufficiency may lead to glomerular hypertrophy and hyperfiltration [43]. The absence of hyperfiltration in the present cohort could be explained by the low prevalence of renal lesions (45% and 20% of the study group had AMLs and cysts respectively) compared to other paediatric cohort studies [12, 44]. Additionally, none of the patients underwent surgical intervention.

Growth of TSC-related renal lesions could impair intraglomerular pressure and overall renal function thus leading to hypertension. However, the mechanisms that link glomerular hyperfiltration to systemic hypertension in TSC are not well understood and further studies are warranted to disentangle their

interrelationship. Abnormal renal hemodynamics, such as increased GFR, could serve as early markers of hypertensive kidney dysfunction in the TSC population. To the best of our knowledge, this is the first cohort study that implemented ABPM in young patients with TSC. Although BP z scores did not correlate with the presence of TSC-associated renal lesions, all patients with ambulatory hypertension had cysts or angiomyolipoma highlighting the importance of ongoing BP surveillance in this population.

The small population size is the main limitation of the present study. Moreover, the cross-sectional design does not allow to establish causal relationships. The study design also did not allow to study the effect of everolimus treatment on GFR and BP which has been previously associated in adults with reduction in the volume of AMLs [45]. On the other hand, objective methods,  $^{99m}\text{Tc}$ -DTPA and ABPM were used to accurately assess kidney function and BP status in the cohort.

In conclusion, the present study provides preliminary evidence that hypertension is prevalent in youth with TSC and that SBP levels have a positive relation with GFR levels within the normal range of  $\text{GFR}_{\text{DTPA}}$  values despite absence of hyperfiltration. Children with AML or cysts would benefit from routine evaluation of their ambulatory BP levels. Still, future prospective studies in larger cohorts are needed to evaluate hypertension progression in youth with TSC.

## List Of Abbreviations

ABPM: ambulatory blood pressure monitoring

AML: angiomyolipoma

BP: blood pressure

cSBP: central systolic blood pressure

CKD: chronic kidney disease

CT: computed tomography

DBP: diastolic blood pressure

DTPA: diethylenetriaminepentaacetic acid

eGFR: estimated glomerular filtration rate

EMMS: estimated marginal means

GFR: glomerular filtration rate

MRI: magnetic resonance imaging

mTOR: mammalian target of rapamycin

PWV: pulse wave velocity

SBP: systolic blood pressure

TSC: tuberous sclerosis complex

TSC-PKD1: tuberous sclerosis complex-Polycystic kidney disease 1

US: ultrasound

## Declarations

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**Non-financial interests:** DZ has served on advisory boards for Novartis and Pharmaten. EV, SS, CS, MK, AA and AN declare that they have no non-financial interests.

**Availability of data and material:** The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Code availability:** N/A

**Authors' contributions:** EV: approved the final version; SS: designed the study, performed statistical analysis and interpretation of data, drafted the initial manuscript, revised and approved the final version; CS: performed data collection, interpretation of data, edited the initial manuscript, approved the final draft; MK: approved the final draft; AA: approved the final draft; AN: edited and approved the final draft; DZ: revised and approved the final version

**Ethics approval:** This study was approved by the Ethics Committee of the Aristotle University of Thessaloniki and was conducted in accordance with the 1964 Helsinki Declaration standards.

**Consent to participate:** Informed consent was obtained from the parents of all the participants.

**Consent for publication:** All have read and approved the paper, have met the criteria for authorship as established by the International Committee of Medical Journals Editors.

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## Figures

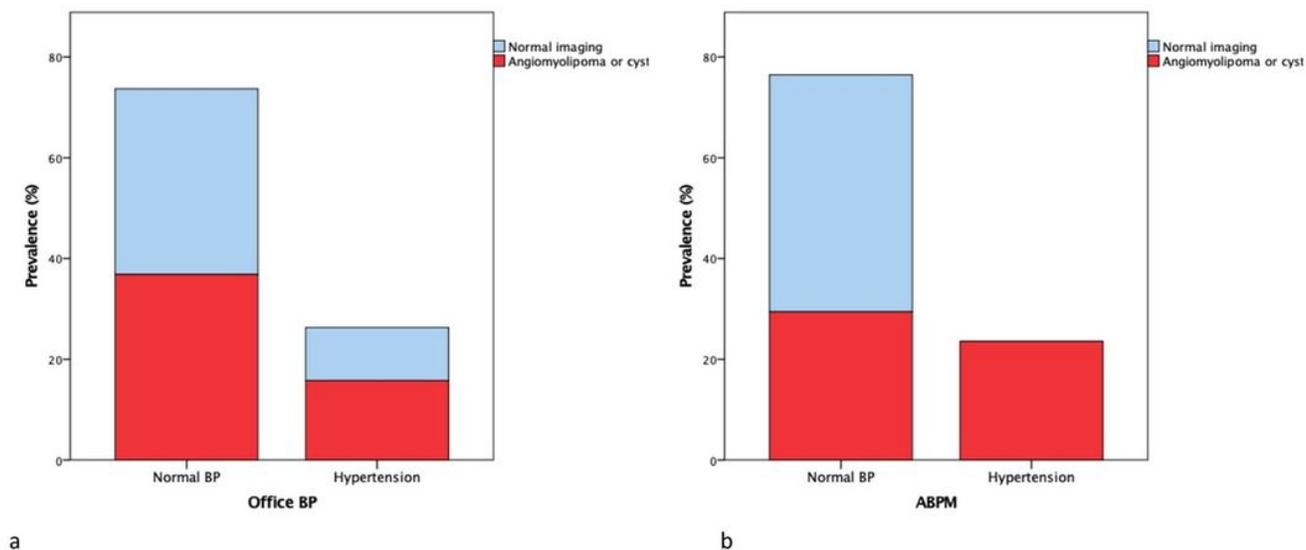


Figure 1

Percentage of patients with office and ambulatory BP hypertension and TSC-related renal lesions.