Whole-Blood Capillary Tube Clotting Time as a Possible Predictor of Hypertensive Disorders in Pregnancy

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Abstract

Background: Hypertensive disorders in pregnancy (HDP) are associated with coagulation abnormalities. However, results of standard coagulation tests in patients with HDP have been inconsistent. Aim: The aim of this study was to determine mean clotting time (CT) in subjects with HDP attending antenatal clinic at Murtala Muhammad specialist Hospital Kano, Nigeria and to assess CT as a possible predictor of HDP.

Materials and Methods: Eighty-four HDP subjects and equal number of normotensive pregnant women were recruited for the study. Blood pressure was measured according to standard protocol. Urinalysis was performed using urine test strips (Medi-Test Combi 9®). Whole-blood CT was determined using capillary tube method. Hypertensive disorders in pregnancy were defined according to the report of National high blood pressure education program working group on high blood pressure in pregnancy. Data were analyzed using IBM SPSS version 23.0. Chi-square test of association and independent t test were used to determine association and difference between categorical and quantitative variables respectively. Pearson's correlation was used to determine relationship between quantitative variables. Multinomial logistic regression was used to determine predictors of HDP. P value ≤ 0.05 was considered statistically significant.

Results: The mean age of the normotensive and HDP subjects was 28.61 ± 5.81 and 30.08 ± 6.80 (t = 1.51, p = 0.132) years. The mean CT and BT of the normotensive and HDP subjects were (192.86 ± 77.96 and 138.57 ± 66.66, t = -4.85, p = 0.001) and (169.40 ±85.38 and 152.50 ± 65.56, t = -1.439, p = 0.152). The normotensive subjects had statistically significant longer mean CT compared to those with gestational hypertension (GH), mild preeclampsia (PE), and severe PE (192.86 ± 77.96, 134.40 ± 41.64, 161.11 ± 78.12, and 122.81 ± 68.73, p = 0.001). Clotting time was positively and negatively correlated with BT, GA, and parity (r = 0.784, p = 0.001; r = -0.508, p = 0.001; r = -0.237, p = 0.030) among the HDP subjects, respectively. When other factors are kept constant, increase in CT was associated with significant lower odds of having GH (OR = 0.983, 95% CI = 0.973-0.993, p = 0.001), mild PE (OR = 0.990, 95% CI = 0.982-0.999, p = 0.022), and severe PE (OR = 0.980, 95% CI = 0.971-0.999, p = 0.001) compared to being normotensive. Equally, CT differentiated HDP subjects from normotensive subjects on receiver operating curve (ROC) (AUC = 0.723, 95% CI = 0.645 – 0.800, p = 0.001).

Conclusion: Hypertensive disorders in pregnancy are associated with shortened whole-blood capillary tube CT, and CT is an independent predictor of HDP.

Keywords: Clotting time, predictor, preeclampsia

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Introduction

Death of women due to pregnancy related complications has continued to rise in developing countries despite reported decline in developed nations. It has been estimated that close to 808 women died on daily basis in 2017 as a result of complications arising from pregnancy and childbirth globally.[1] Of these 808 deaths, 540 (representing about 66% of the global maternal death in 2017) occurred in sub-Saharan Africa while 225 were in southern Asia. Most of these deaths were due to preventable diseases such as hemorrhages, hypertension, and infections.[2]

While the number of women dying from complications of pregnancy and childbirth declined by 35% from 2000 to 2017 globally, the problem persists in sub-Saharan Africa and other developing nations.[1] Indeed, a recent WHO estimate put the lifetime risk of a woman dying from complications of pregnancy and childbirth in a developing Nation as 120 times that of a developed one.[1] Nigeria was estimated to have contributed about 670,00 maternal deaths accounting for 23% of the global burden of the problem in 2017.[1]

One of the major causes of maternal death in developing Nations especially sub-Saharan Africa is HDP. A constellation of pregnancy related hypertension, HDP are made up of gestational hypertension (GH), preeclampsia (PE), chronic hypertension with superimposed preeclampsia, and eclampsia. Together they complicate about 3 – 10% of pregnancies globally and even higher in sub-Saharan Africa.[2,3] In a systematic review and meta-analysis of 82 studies from 24 African countries consisting of 854,304 participants, Nyaga *et al*.[3] reported a pooled prevalence of HDP in Africa to be 49.8%.[3] In Nigeria, prevalence of HDP varies from one study and region to another. A prevalence of 17% was reported from a study in northern part of the country while 10.3% was reported by another study from the south.[4,5]

Hypertensive disorders in pregnancy are associated with increased risk of cesarean delivery, preterm delivery and neonatal admissions, and obstetric hemorrhages.[6] Pregnancy is associated with hypercoagulability especially in third trimester however, HDP exacerbates the coagulation abnormalities thus predisposing to prothrombotic state.[7,8] Prothrombin time (PT) and activated partial prothrombin time (aPTT) have traditionally been used to assess coagulopathy in patients with HDP. However, coagulation studies in patients with HDP using PT and aPTT have been inconsistent and sometimes considered of no clinical relevance.[9,10] And, while platelet count has been widely used to assess thrombotic events especially in patients with severe PE, the results are often conflicting.[11,12] Whole-blood capillary tube CT is a simple and inexpensive test that can be performed quickly by even lesser skilled health workers. Its validity in predicting coagulopathy has been established in patients with snakebite injuries.[13] It can therefore serve as an alternative to the standard coagulation tests in evaluation of patients with HDP. The aim of this study was to determine mean CT in subjects with HDP attending antenatal clinic at Murtala Muhammad specialist Hospital Kano, Nigeria and to assess CT as a possible predictor of HDP.

Materials and Methods

Study area and selection of participants

This cross-sectional comparative study was conducted at the Murtala Muhammad specialist Hospital, Kano, Nigeria between September and October 2019. The hospital is a secondary health facility that provides both general and specialized care. The antenatal clinic is run on weekdays with the exception of Fridays. All pregnant women with GH and PE were considered for recruitment into the study. Subjects with chronic hypertension, history of bleeding disorders, and those who declined informed consent were excluded from the study. Equal number of normotensive pregnant women were recruited from the same clinic as controls.

Minimum sample size was calculated using the formula for sample size in health studies by Lwanga and Lemeshow, [14] and mean ± SD of PT by Awolola and Enaruna.[15]

$$n = 2 \times (Z_{\alpha} + Z_{1-\beta})^2 SD^2 / U_1 - U_2$$

where:

n = minimum sample size

Z_{α} = standard normal deviate corresponding to 95% confidence interval = 1.96

$Z_{1-\beta}$ = power = 0.84

SD = standard deviation from a previous study = 5.59

U_1 = mean PT of one sample from previous study = 18.80 sec

U_2 = mean PT of the other sample from previous study = 12.49 sec

$N = 2 \times (1.96 + 0.84)^2 (5.59)^2/(18.80\text{-}12.49) = 63.$

Systematic sampling technique using sampling frame of 800 (weekly patient turnout of 200 making a monthly turnout of 800) and sample size of 63 was used to recruit subjects into the study.

Ethical clearance

Ethical approval was obtained from the Ethics Research Committee of Kano state ministry of health with reference number MOH/Off/797/T.I/1538. Permission to conduct the study was also sought from the management of the hospital and subjects were requested to sign an individual informed consent form.

Data Collection

A data capture form was used to collect information on sociodemographic characteristics and HDP related information of the subjects. Blood pressure was measured using mercury sphygmomanometer (Accoson™ Ltd., Ayrshire, UK) and 3M™ Littmann® stethoscope (3M Littmann®, Minnesota, USA). Systolic blood pressure was taken at the first appearance of Korotkoff sound (Korotkoff I) while diastolic blood pressure was taken at the disappearance of the sound (Korotkoff V). Mean arterial blood pressure was calculated from the relation:

$$MAP = DBP + 1/3\ (SBP - DBP).$$

Urinalysis was performed on fresh early morning urine sample using urine test strips (Medi-Test Combi 9®). The test was performed according to manufacturer's guidelines. Proteinuria was graded as mild = 1 +, moderate = 2++, and severe = 3+++.

Clotting time was determined using whole-blood capillary tube method. It involves drawing blood into a non-heparinized capillary tube and allowing it to coagulate while noting the duration of time, in seconds, between the collection of blood and formation of the clot. A finger of each subject was first cleaned using cotton wool soaked in methylated spirit. A non-heparinized capillary tube was then applied to the pricked fingertip to draw blood into the tube by capillary action. The time at which the blood starts to appear in the tube was noted and thereafter the tube was broken at intervals of 30 seconds until the blood forms a jelly-like material denoting coagulation. Clotting time was then calculated as number of broken pieces of the tube multiplied by 30, in seconds.

Bleeding time was determined using Whatman filter paper as described by Duke.[16] It involves pricking the finger with sterile lancet to cause bleeding, the time taken for the bleeding to stop is then measured which is the BT. After cleaning a finger of the subject with methylated spirit and allowing it to air dry, a deep prick was made on the tip using sterile lancet. The free-flowing blood was then wiped off by touching the pricked fingertip with Whatman filter paper after every 30 seconds until the bleeding stopped. The number of times the blood was wiped off was multiplied by 30 and BT recorded in seconds.

Working definitions of GH, mild PE, and severe PE were adopted from the report of National high blood pressure education program working group on high blood pressure in pregnancy of 2000.[17] Gestational hypertension was defined as systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure of $\geq$ 90 mmHg in a previously normotensive pregnant woman after 20 weeks gestation in the absence of proteinuria. Mild PE was defined as SBP $\geq$ 140 mmHg or DBP $\geq$ 90 and proteinuria of 1+ or 2++ while severe PE as SBP $\geq$ 160 mmHg or DBP $\geq$ 110 mmHg and proteinuria of 3+++.

Statistical analysis

Data were analysed using IBM SPSS version 23.0 (IBM, Armonk, New York, USA). Chi-square test of association was used to determine association between categorical variables while mean difference in quantitative variables between the normotensive and HDP subjects was determined by independent t test. Similarly, one-way analysis of variance with Bonferroni post hoc was used to determine mean difference in quantitative variables between normotensive, GH, mild PE, and severe PE subjects. Pearson's correlation was used to determine relationship between clotting and bleeding time and other quantitative variables in HDP subjects. Multinomial logistic regression was used to determine predictors of HDP. P value $\leq$ 0.05 was considered statistically significant. Results were presented as frequencies, percentages, mean ± SD, coefficients, and odd ratios.

Results

Sociodemographic characteristics of the subjects

A total of 168 subjects consisting of 84 normotensive and 84 HDP pregnant women were recruited for the study.

The mean age of the normotensive and HDP subjects was 28.61 ± 5.81 and 30.08 ± 6.80 (t = 1.51, p = 0.132) years, respectively. Majority of the subjects in both groups had at least primary school education (7(91.67%) and 76(90.48%), X^2 = 0.87, p = 0.832). Similarly, most of the subjects in both groups were married as at the time of the study and there was statistically significant association between marital status and HDP (X^2 = 6.44, p = 0.040). Majority of the subjects in both groups were Hausa with few Igbos, Yorubas, and other ethnicities. There was statistically significant association between ethnicity and HDP (X^2 = 10.75, p = 0.013). Majority of the subjects in both groups were multigravidas or grand multigravidas (91.7% and 89.3%, X^2 = 0.413, p = 0.813, for controls and cases, respectively). Results of sociodemographic characteristics of the subjects are shown on tables 1.

Mean clinical and laboratory parameters of the subjects

The normotensive group had statistically significant lower systolic (114 ± 11.90 and 162 ± 21.69, t = 17.82, p = 0.001), diastolic (72 ± 8.69 and 96 ± 13.54, t = 13.35, p = 0.001), and mean arterial blood pressure (86 ± 8.35 and 118 ± 14.34, t = 17.49, p = 0.001) compared to the HDP group. The normotensive subjects had statistically significant longer CT than the HDP subjects (192.86 ± 77.96 and 138.57 ± 66.66, t = -4.85, p = 0.001). However, there was no statistically significant difference in BT (169.40 ±85.38 and 152.50 ± 65.56, t = -1.439, p = 0.152) and gestational age (GA) (7.31 ± 1.40 and 7.19 ± 1.37, t = -0.56, p = 0.577) between the normotensive and the HDP subjects, respectively – table 2.

The normotensive subjects had statistically significant longer mean CT compared to those with GH, mild PE, and severe PE (192.86 ± 77.96, 134.40 ± 41.64, 161.11 ± 78.12, and 122.81 ± 68.73, p = 0.001). Bonferroni post hoc further revealed that the difference lies between normotensive subjects and those with GH (p = 0.003) and between normotensive and severe PE subjects (p = 0.001). In contrast, there was no statistically significant difference in BT among the 4 groups (169.40 ± 85.38, 152.40 ± 47.17, 168.33 ± 65.03, 139.22 ± 76.41, p = 0.243) table 3.

Relationship between CT, BT and other clinical parameters of the HDP subjects

Clotting time was positively and negatively correlated with BT, GA, and parity (r = 0.784, p = 0.001; r = -0.508, p = 0.001; r = -0.237, p = 0.030) among the HDP subjects, respectively. Similarly, BT was positively and negatively correlated with CT and GA (r = 0.784, p = 0.001; r = -0.621, p = 0.001) among the HDP subjects, respectively – table 4.

When those variables that were correlated with CT were included in multiple regression analysis together with age, the variables (age, MAP, GA, and parity) accounted for 29% of variance in CT and the overall model was statistically significant (F[3, 80] = 10.816, R^2 = 29%, p = 0.001). However, only GA emerged as an independent predictor of CT (t = -5.366, p = 0.001). Similarly, when BT was regressed against age, MAP, GA, and parity, the variables accounted for 40% of the variance in BT and the model was statistically significant (F[3, 80] = 17, R^2 = 40%, p = 0.001) but only GA emerged as an independent predictor of BT (t = -7.167, p = 0.001).

When other factors are kept constant, increase in CT was associated with significant lower odds of having GH (OR = 0.983, 95% CI = 0.973-0.993, p = 0.001), mild PE (OR = 0.990, 95% CI = 0.982-0.999, p = 0.022), and severe PE (OR = 0.980, 95% CI = 0.971-0.999, p = 0.001) compared to being normotensive. Equally, CT differentiated HDP subjects from normotensive subjects on receiver operating curve (ROC) (AUC = 0.723, 95% CI = 0.645 – 0.800, p = 0.001) – table 5.

Table 1: Sociodemographic characteristics and parity of the normotensive and HDP subjects

Variable		Normotensives N (%)	HDP N (%)	Test Statistic	P value
Level of education				0.87	0.832
	Informal	7 (8.3)	8 (9.5)		
	Primary	17 (20.2)	19 (22.6)		
	Secondary	43 (51.2)	37 (44.0)		
	Tertiary	17 (20.2)	20 (23.8)		
Marital status				6.44	0.040*
	Married	77 (91.7)	66 (78.6)		
	Divorced	5 (6.0)	9 (10.7)		
	Widow	2 (2.4)	9 (10.7)		
Ethnicity				10.75	0.013*
	Hausa	80 (95.2)	68 (81.0)		
	Igbo	0 (00.0)	7 (8.3)		
	Yoruba	2 (2.4)	7 (8.3)		
	Others	2 (2.4)	2 (2.4)		
Occupation				2.69	0.261
	Housewife	33 (39.3)	34 (40.5)		
	Trader	48 (57.1)	42 (50.0)		
	Civil servant	3 (3.6)	8 (9.5)		
Parity				0.413	0.813
	Primigravida	7(8.3)	9(10.7)		
	Multigravida	46(54.76)	47(55.95)		
	Grand multigravida	31(36.90)	28(33.33)		

* *Statistically significant variable*

Table 2: Mean clinical and laboratory parameters of the subjects

Variable	Normotensives Mean ± SD	HDP Mean ± SD	Test Statistic	P value
Age (Years)	28.61 ± 5.81	30.08 ± 6.80	1.51	0.132
SBP (mmHg)	114 ± 11.90	162 ± 21.69	17.82	0.001*
DBP (mmHg)	72 ± 8.69	96 ± 13.54	13.35	0.001*
MAP (mmHg)	86 ± 8.35	118 ± 14.34	17.49	0.001*
BT (seconds)	169.40 ± 85.38	152.50 ± 65.56	-1.44	0.152
CT (seconds)	192.86 ± 77.96	138.57 ± 66.66	-4.85	0.001*

**Statistically significant variable, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, MAP = Mean arterial pressure, BT = Bleeding time, CT = Clotting time, GA = Gestational age, SD = standard deviation*

Table 3: Comparison of mean CT and BT among the normotensive, GH, mild and severe PE subjects

Variable	Normotensive Mean ± SD	GH Mean ± SD	Mild PE Mean ± SD	Severe PE Mean ± SD	F	P value
CT (sec)	192.86 ± 77.96	134.40 ± 41.64	161.11 ± 78.12	122.81 ± 68.73	9.368	0.001*
BT (sec)	169.40 ± 85.38	152.40 ± 85.38	168.33 ± 65.03	139.22 ± 22	1.406	0.243

**Statistically significant variable, CT = clotting time, BT = bleeding time, GH = gestational hypertension, PE = preeclampsia.*

Table 4: Relationship between CT, BT and other clinical parameters of the subjects with HDP

	Clotting time				Bleeding time			
	Correlation		Multiple regression		Correlation		Multiple regression	
Variable	r	p	t	p	r	p	t	p
Age (years)	-0.071	0.520	-1.053	0.295	-0.048	0.665	-0.908	0.366
SBP (mmHg)	-0.191	0.082	-	-	-0.165	0.135	-	-
DBP (mmHg)	-0.104	0.345	-	-	-0.066	0.550	-	-
MAP (mmHg)	-0.162	0.141	-1.590	0.116	-0.125	0.259	-1.249	0.215
BT/CT (sec)	0.784	0.001*	-	-	0.784	0.001*	-	-
GA (months)	-0.508	0.001*	-5.366	0.001*	-0.621	0.001*	-7.167	0.001*
Parity	-0.237	0.030*	-	-	-0.180	0.101	-0.964	0.338

**Statistically significant variable, SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, GA = gestational age, BT = Bleeding time, CT = Clotting time, r = Pearson's correlation*

Table 5: Relationship between HDP categories and other parameters of the subjects

Dependent variable	Predictor	Test statistic		
		OR	95% CI	P value
GH	Age (years)	1.065	0.993-1.142	0.080
	GA (months)	0.920	0.661-1.280	0.620
	CT (sec)	0.983	0.973-0.993	0.001*
	BT (sec)	1.007	0.998-1.016	0.111
Mild PE	Age (years)	1.026	0.958-1.100	0.460
	GA (months)	0.906	0.661-1.242	0.541
	CT (sec)	0.990	0.982-0.999	0.022*
	BT (sec)	1.006	0.998-1.014	0.126
Severe PE	Age (years)	1.025	0.960-1.094	0.457
	GA (months)	1.008	0.748-1.359	0.959
	CT (sec)	0.980	0.971-0.990	0.001*
	BT (sec)	1.005	0.997-1.013	0.232

**Statistically significant variable, HDP = hypertensive disorders in pregnancy, GH = gestational hypertension, PE = preeclampsia, GA = gestational age, CT = clotting time, BT = bleeding time, OR = odd ratio, CI = confidence interval.*

Discussion

This study has demonstrated significant shorter whole-blood capillary tube CT among HDP subjects compared to normotensive subjects. This difference persisted even when the HDP subjects were segregated into GH, mild PE, and severe PE groups. Most studies use PT and aPTT to assess coagulation in HDP patients while very few, if any, uses whole-blood capillary tube CT. This finding, of shorter capillary tube CT, is similar to what was reported by Mtali *et al*. [8] who reported shorter PT among HDP subjects compared to normotensive controls. Similarly, Wodzicki *et al*. [18] found shorter PTT among HDP subjects compared to their normotensive controls. It however contrasts what was reported by Bolaji *et al*. [19] in their prospective study of coagulation profile of severe preeclamptic and eclamptic patients in Ilorin, north-central Nigeria. They reported that, even though mean international normalized ratio (INR) and aPTT for both preeclamptic/eclamptic subjects and normotensive controls were within normal limits, the former had statistically significant longer aPTT. Similarly, Lakshmi [20] reported prolonged CT among HDP subjects compared to normotensive controls in an Indian population. However, Awolola and Enaruna [15] found prolongation of PT in patients with severe PE and eclampsia only when there was associated thrombocytopenia and the degree of prolongation was directly proportional to the degree of thrombocytopenia. The traditional tests of coagulation, PT and aPTT, are not meant for testing clinical coagulopathy. Prothrombin time assesses vitamin K-dependent clotting factors, factors II, V, VII, and X, and is use clinically to monitor patients on warfarin.[21] Activated partial thromboplastin time on the other hand assesses factors VIII, XI, and XI and is use clinically to monitor patients on heparin.[21] This might explain the reason for the inconsistency in the results of PT and aPTT in subjects with HDP. Indeed, Szecs *et al*. [22] reported that standard coagulation tests like PT, INR, and aPTT do not change during pregnancy or rarely does so. Pregnancy, especially in the third trimester, is associated with enhanced production of thrombin, the final common end product of both intrinsic and extrinsic coagulation pathways, leading to a hypercoagulable state and hence shortened PT, aPTT, and CT.[23] Specifically, serum levels of fibrinogen, factors VII, VIII, IX, X, XII, and von Willebrand factor are increased in pregnancy while those of factors XIII, protein S, and platelet count are decreased.[21] The hypercoagulable state of pregnancy is exaggerated in patients with HDP due to the enhanced thrombin production coupled with platelet activation, endothelial dysfunction and recruitment of proinflammatory cytokines.[23] This leads to initial shortening of CT but as the disease progresses to a more severe form there is rapid consumption of coagulation factors with consequent prolongation of CT. Whole-blood capillary CT and BT were negatively correlated with GA among the HDP subjects in this study. This implies that both CT and BT shorten as pregnancy progresses. As pregnancy progresses thrombin production and platelet activation also increase thus shortening the time required for blood to clots and for bleeding to stops.

Multinomial logistic regression analysis revealed whole-blood capillary CT as an independent predictor of HDP categories. It also had statistically significant higher AUC on ROC. Many studies have suggested various predictors of PE among HDP patients. However, none, to our knowledge, has reported whole-blood capillary CT as a predictor of HDP among pregnant women. Paternoster *et al*.[24] reported albumin excretion rate as an independent predictor of PE among HDP subjects. Maternal serum uric acid and calcium have also been reported as predictors of HDP.[25] Others have reported brachial artery flow mediated dilation and pulsatility index change, bedside cardiovascular maternal interrogation in the first trimester, first trimester blood pressure and serum soluble fms-like tyrosine kinase-1, and placental growth factor as possible predictors of HDP.[26,27,28,29]

Hypertensive disorders in pregnancy are a group of diseases that are clinically characterized by elevation of blood pressure with or without presence of protein in the urine in later half of pregnancy. They include GH, PE, chronic hypertension with superimposed PE, and eclampsia.[2] The disease run a predictable course from GH to mild and severe PE and subsequently eclampsia. The exact mechanism mediating development of HDP is not known, however, placental hypoperfusion as a result of poor cytotrophoblastic invasion of uterine spiral arteries is thought to be responsible for the generalized induction of endothelial dysfunction, inflammation, platelet activation and abnormal coagulation that characterize the disease.[30] Cytotrophoblastic invasion

of uterine spiral arteries is believed to be essential for converting the otherwise resistant arteries into low resistance and high flow arteries that are required for proper foeto-maternal circulation.[30] One of the consequences of this failure of cytotrophoblastic invasion is the activation of platelets and other coagulation factors.[31] However, the degree of clinical haemostatic abnormalities varies directly with the severity of the disease. Patients with severe PE and eclampsia tend to manifest worst haemostatic abnormalities while those with GH or mild PE tend to have mild or no haemostatic problems. There has been reported difficulty in predicting patients that would have haemostatic abnormalities in the course of the disease because the standard coagulation tests that are often used for this purpose correlate poorly with clinical outcomes.[10,21] While platelet count has provided promising results in detecting patients that will likely develop haemostatic abnormalities, it is mostly significant in patients with severe form of the disease and may therefore not be appropriate for risk stratification.[32] Whole-blood capillary CT, a cheap and simple test that can be performed by lesser skilled health workers, could provide the needed alternative to the standard coagulation tests in risk stratification and prognostication in patients with HDP.

Conclusion

Hypertensive disorders in pregnancy are associated with shortened whole-blood capillary tube CT, and CT is an independent predictor of HDP. Whole-blood capillary tube CT should be explored as a possible predictor of HDP.

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Conflict of interest

We declare that none of us has any conflict of interest in this work.

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