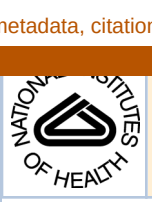

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Decades after the Cooperative Study: A Re-examination of Systemic Blood Pressure in Sickle Cell Disease

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Abstract

Previous studies report lower systemic blood pressures in patients with sickle cell disease (SCD) than in appropriate controls. The etiology of the lower systolic and diastolic blood pressures (SBP and DBP) remains uncertain. Blood pressure measurements from patients followed at our center (UNC cohort) were compared with values obtained from the Cooperative Study of Sickle Cell Disease (CSSCD) and healthy control subjects. Associations of SBP and DBP with clinical and laboratory covariates were performed in the UNC cohort. Patients in the UNC cohort were significantly older and had a higher BMI than those in the CSSCD ($p < 0.0001$). There were no differences in the SBP and DBP between SCD patients in the UNC cohort and control subjects. In the SS/SD/Sβ^0 thalassemia group, SBP was higher in the UNC cohort than in the CSSCD ($p < 0.0001$). On multivariate analysis, significant correlations were noted between SBP and age, BMI, history of hypertension and absolute neutrophil count. Compared with historic controls, SBP was significantly higher in our SCD patient cohort. There was no difference when blood pressure was compared between our patient cohort and control subjects. Age, BMI and neutrophil count may contribute to the modulation of SBP in SCD.

Keywords

Sickle cell disease; Systemic Blood pressure; Hemolysis; Absolute neutrophil count; Body mass index

Multiple studies have reported that patients with SCD have lower systemic blood pressures when compared with age-, sex-, and race-matched controls (1–4). This was confirmed by the Cooperative Study of Sickle Cell Disease (CSSCD), a natural history study of SCD in the United States (4). With the recent advances in the care of patients with SCD, we compared systolic and diastolic blood pressure (SBP and DBP) measurements in a patient cohort followed at our clinical center with values obtained in the CSSCD and from healthy, control subjects. Furthermore, we evaluated the association of SBP and DBP with clinical and laboratory variables in our patient cohort.

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Blood pressure measurements were obtained in 156 SCD patients in the UNC cohort and 1232 patients in the CSSCD cohort. Patients in the UNC cohort were older and had a higher BMI than patients in the CSSCD cohort (Table 1). The UNC cohort also had a significantly higher proportion of patients with a diagnosis of hypertension and patients on antihypertensive medications.

Patients in the UNC and CSSCD cohorts were categorized into 2 groups based on presumed disease severity - SS/SD/Sβ^0 thalassemia and SC/Sβ^+ thalassemia, without consideration of alpha and delta thalassemia status. There were 129 patients in the SS/SD/Sβ^0 thalassemia group (83%) and 27 patients in the SC/Sβ^+ thalassemia group (17%) in the UNC cohort, with 899 patients in the SS/SD/Sβ^0 thalassemia group (73%) and 333 patients in the SC/Sβ^+ thalassemia group (27%) in the CSSCD cohort. The SBP in the SS/SD/Sβ^0 thalassemia group was significantly higher in the UNC cohort than in the CSSCD cohort (122 ± 15 mm Hg vs. 113 ± 14.5 mm Hg, $p < 0.0001$), but there was no difference in the DBP when both cohorts were compared (69 ± 10.5 mm Hg vs. 69 ± 10.5 mm Hg; $p = 0.8$). Similarly, in the SC/Sβ^+ thalassemia group, the SBP was significantly higher in the UNC cohort (131 ±12 mm Hg vs. 116 ±15.5 mm Hg; $p < 0.0001$), but no difference was observed when the DBP in both cohorts were compared. When all the SCD patients were stratified by age, the SBP in the UNC cohort was higher in male patients in the 35 – 44-year age group and female patients in the 18 – 24-year, 25 – 34-year and 35 – 44-year age groups compared with the CSSCD cohort (supplementary data, Figure 1; Table 1).

We compared the SBP and DBP in SCD patients in the UNC cohort with values from 24 healthy, African-American control subjects without SCD (genotype- AA; median age: 37 years [IQR: 26, 49 years]; BMI: 30.5 [IQR: 25.6, 36.7]). No significant differences were observed in the SBP or DBP when both groups were compared. Furthermore, there were no significant differences in the SBP and DBP when patients in the SS/SD/Sβ^0 group were compared with healthy controls. However, patients in the SC/Sβ^+ group had significantly higher SBP when compared with healthy controls (130.9 ± 12.1 mm Hg vs. 120.9 ± 11.3 mm Hg, $p = 0.01$), although no difference was observed in the DBP when both groups were compared.

Significant correlations were observed between SBP and age ($\rho = 0.37$, $p < 0.0001$) and BMI ($\rho = 0.41$, $p < 0.0001$) (Table 2). Patients with a history of hypertension as well as those on antihypertensive therapy had significantly higher SBP than those without such history or therapy. Modest correlations were observed between SBP and white blood cell count, hemoglobin, reticulocyte count, lactate dehydrogenase, total bilirubin, indirect bilirubin, and placenta growth factor (PIGF) (Table 3). There were significant correlations between DBP and age and BMI. Modest correlations were also observed between DBP and hemoglobin, platelet count, reticulocyte count, total bilirubin, and indirect bilirubin. There were no significant associations between the evaluated SCD-related clinical complications and either SBP or DBP.

After controlling for other covariates, SBP was significantly associated with age (estimate: 0.30, $p = 0.0026$), BMI (estimate: 0.76, $p < 0.0001$), prior diagnosis of hypertension (estimate: 6.48, $p = 0.027$), absolute neutrophil count (estimate: −1.18, $p = 0.023$), but not with lactate dehydrogenase (estimate: 0.0017, $p = 0.49$) or hemoglobin (estimate: 1.01, $p = 0.14$). This means that we expect an increase in SBP by 0.30 mm Hg for every 1 year increase in age; an increase in SBP by 0.76 mm Hg for every 1 kg/m^2 increase in BMI; and a decrease in SBP by 1.18 mm Hg for every 1×10^9/L increase in absolute neutrophil count. For a binary response such as prior diagnosis of hypertension, the estimated value of 6.48 indicates that having a history of hypertension is predicted to result in an increase in SBP of 6.48 mm Hg compared to no history of hypertension. Similarly, after controlling for other

covariates, DBP was significantly associated with age (estimate: 0.25, p = 0.0004), hemoglobin (estimate: 1.71, p = 0.0021), history of smoking (estimate: −4.96, p = 0.0074), but not with lactate dehydrogenase (estimate: −0.00096, p = 0.62).

Despite reported lower systemic blood pressures, patients with higher SBP relative to the SCD population appear to be at higher risk for stroke (4, 5), echocardiography-defined pulmonary hypertension (6), albuminuria (7, 8), and increased mortality (4). Given the risk of clinical complications despite the apparent lower blood pressures than those obtained in control populations, it is uncertain whether the usual recommendations for the diagnosis of hypertension apply to patients with SCD. We found a significantly higher SBP in SCD patients followed at our center than was observed in the CSSCD. Furthermore, there were no significant differences when the SBP and DBP in SCD patients followed at our center were compared with healthy, control subjects. This finding is similar to that by Thompson and colleagues which showed no difference in the SBP between a cohort of SCD patients and healthy controls in Jamaica (8).

Consistent with a previous report (4), we found an association between SBP and both age and BMI. While patients in the UNC cohort were significantly older than those in the CSSCD, SBP and DBP values in the UNC cohort were higher when specific age groups were compared, suggesting that age is not the primary reason for the blood pressure differences in both patient cohorts. With the known association between weight and systemic blood pressure (9), the higher BMI in the UNC cohort may contribute to their higher blood pressure values compared to patients in the CSSCD.

Although it has been suggested that lower systemic blood pressures in SCD may be a result of higher urinary sodium loss due to hyposthenuria (3, 4), intravenous salt loading had no effect on blood pressure (10). Furthermore, individuals with sickle cell trait, who also exhibit hyposthenuria, do not have lower blood pressures than age- and race-matched controls (11). There are conflicting reports on the association of anemia with systemic blood pressure in SCD (3, 4, 12). We observed modest associations between markers of hemolysis and both SBP and DBP on univariate analysis, but only hemoglobin remained significantly associated with DBP on multivariate analysis, suggesting that hemolysis may not play a substantial role in blood pressure modulation in SCD. The inverse correlation between SBP and PlGF on univariate analysis suggests that PlGF may play a role in the regulation of blood pressure in SCD. This angiogenic growth factor is higher in SCD patients than in control subjects (13). As in preeclampsia (14), PlGF may contribute to the modulation of systemic blood pressure in SCD.

Depletion of neutrophils in healthy mice reduces SBP and produces an impairment of vascular constriction studied ex vivo (15). This effect was attributed to neutrophil suppression of interferon-mediated inducible nitric oxide synthase expression. The reason for the contradictory finding in SCD patients in our study is uncertain. SCD is referred to as a chronic inflammatory state (16) and patients exhibit elevated leukocyte counts and abnormal activation of various cellular elements (17) even in the non-crisis, “steady state”. Leukocytosis is also a risk factor for multiple complications, including acute chest syndrome (18) hemorrhagic stroke (5), vasoocclusive crises (19) and increased mortality (20). Our study suggests that the inflammatory state, by possibly increasing the rate of complications and disease severity, may produce lower blood pressures in patients with SCD.

This study was not primarily designed to evaluate systemic blood pressure in SCD. Blood pressure measurement was performed using different techniques in our patient cohort and the CSSCD. Our patients were recruited from a specialty clinic at a tertiary care medical

center, and may not represent all patients with SCD. As with all cross-sectional studies, this analysis demonstrates associations, but cannot prove causation.

In conclusion, patients with SCD in our cohort have significantly higher systemic blood pressures compared with a historical cohort. The blood pressures of our patient cohort are not significantly different when compared with control subjects. SBP is associated with age, BMI, history of hypertension and inversely associated with absolute neutrophil count.

MATERIALS AND METHODS

Study Subjects

The study subjects represent a cohort of patients followed at the Adult Sickle Cell Clinic at the University of North Carolina, Chapel Hill (UNC cohort). Data were obtained as part of a study to investigate the pathophysiology of pulmonary hypertension in SCD (21). Patients were fassessed while in the non-crisis, “steady state;” had not experienced an episode of acute chest syndrome in the 4 weeks preceding enrollment; and had no clinical evidence of congestive heart failure. The healthy control subjects had no known medical conditions, were not taking any medications, and were recruited by advertisement. The study was approved by the Institutional Review Board at UNC, Chapel Hill and written informed consent was obtained from all participants.

Assessment of Clinical Complications

The presence or history of SCD-related clinical complications, systemic hypertension as well as ongoing use of antihypertensive medications was ascertained at the time of evaluation, combined with a detailed review of the medical records. Acute pain episodes (or pain crises), acute chest syndrome, stroke and other SCD-related complications were defined using standard definitions (5, 22, 23). Tricuspid regurgitant jet velocity was measured by Doppler echocardiography as previously described (24).

Clinical and Laboratory Measurements

Height, weight, blood pressure, and laboratory studies in SCD patients and healthy control subjects were measured during the course of a single visit to the Clinical Translation and Research Center. Body mass index (BMI) was calculated as weight/height^2, in units of kg/m^2. Seated blood pressure was measured with an automated device (GE Dinamap Carescape V100, Frelburg, Germany (25); GE Dinamap Procare400 , Frelburg, Germany (25, 26); Critikon Dinamap 8100T, Tampa, FL; Welch-Allyn 53NT0, Meaverton, Oregon) following a minimum of 10 minutes of rest. Quantification of human soluble vascular cell adhesion molecule-1 (R&D systems, Minneapolis, MN), soluble fms-like tyrosine kinase-1 (R&D systems, Minneapolis, MN) and PlGF (R&D systems, Minneapolis, MN) was accomplished using commercially available ELISA kits. Samples were assayed in duplicate and according to manufacturer’s instructions. Routine blood and urine studies were performed by the McClendon Clinical Laboratory at UNC Hospitals.

Cooperative Study of Sickle Cell Disease

The CSSCD was a prospective, natural history study in SCD that enrolled patients at 23 clinical centers in the United States from 1978 to 1988 (Phase 1) (27). Blood pressure measurements, clinical data, and laboratory data were collected on all patients older than 2-years during their initial visit and not during acute painful episodes. Single blood pressure measurements were obtained in the sitting position, following at least 5 minutes of rest, using mercury sphygmomanometers. The systolic and diastolic pressures were reported as the first and fifth Korotkoff sounds, respectively (4). Hemoglobin analysis was performed at the Centers for Disease Control and the genotypes included in the analysis were SS, Sβ^0,

SSα, $S\beta^0\alpha$, $S\beta^0\delta$, SC, $S\beta^+$, and other sickle hemoglobinopathies. Acute chest syndrome included only patients with a history of pneumonia. We present results on patients older than 18-years who were on the full protocol and had baseline SBP and DBP measurements. Subjects with missing blood pressure data were excluded from the analyses.

Statistical Methods

Wilcoxon Rank Sum tests were used to compare continuous variables in the UNC cohort to the CSSCD cohort. Categorical variables were compared using Fisher's exact tests. Using only the UNC cohort, the association of 25 clinical and laboratory variables with both SBP and DBP was explored using Spearman's correlation coefficients for continuous variables and Wilcoxon Rank Sum tests for categorical variables. A p-value < 0.05 was considered statistically significant. Reported p-values are considered 'nominal' and are for individual tests, unadjusted for multiple comparisons because of the exploratory nature of this study. For the UNC cohort, based on available sample size ($N \geq 140$), multivariable analyses were performed using multiple regression to assess the associations between clinical and laboratory variables that were associated with SBP and DBP in univariate analyses ($p < 0{\cdot}15$). Backwards elimination using F statistics was used to select the best model. Given the importance of lactate dehydrogenase, this variable was added to both models since it was not selected. Similarly, hemoglobin was added to the SBP model. Statistical analyses were performed with SAS statistical software, version 9.2 (SAS Institute Inc., Cary, NC).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. de Jong PE, Landman H, van Eps LW. Blood pressure in sickle cell disease. Arch Intern Med. 1982; 142:1239–1240. [PubMed: 7092436]
2. Grell GA, Alleyne GA, Serjeant GR. Blood pressure in adults with homozygous sickle cell disease. Lancet. 1981; 2:1166. [PubMed: 6118599]
3. Johnson CS, Giorgio AJ. Arterial blood pressure in adults with sickle cell disease. Arch Intern Med. 1981; 141:891–893. [PubMed: 7235808]
4. Pegelow CH, Colangelo L, Steinberg M, Wright EC, Smith J, Phillips G, Vichinsky E. Natural history of blood pressure in sickle cell disease: risks for stroke and death associated with relative hypertension in sickle cell anemia. Am J Med. 1997; 102:171–177. [PubMed: 9217567]
5. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, Wethers DL, Pegelow CH, Gill FM. Sickle Cell Disease tCSo. Cerebrovascular Accidents in Sickle Cell Disease: Rates and Risk Factors. Blood. 1998; 91:288–294. [PubMed: 9414296]
6. Gladwin MT, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, Minter K, Brown B, Coles WA, Nichols JS, Ernst I, Hunter LA, Blackwelder WC, Schechter AN, Rodgers GP, Castro O, Ognibene FP. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med. 2004; 350:886–895. [PubMed: 14985486]
7. Guasch A, Cua M, Mitch WE. Early detection and the course of glomerular injury in patients with sickle cell anemia. Kidney international. 1996; 49:786–791. [PubMed: 8648921]

8. Thompson J, Reid M, Hambleton I, Serjeant GR. Albuminuria and renal function in homozygous sickle cell disease: observations from a cohort study. Archives of Internal Medicine. 2007; 167:701–708. [PubMed: 17420429]
9. Dyer AR, Elliott P. The INTERSALT study: relations of body mass index to blood pressure. INTERSALT Co-operative Research Group. Journal of human hypertension. 1989; 3:299–308. [PubMed: 2810326]
10. Hatch FE, Crowe LR, Miles DE, Young JP, Portner ME. Altered vascular reactivity in sickle hemoglobinopathy. A possible protective factor from hypertension. Am J Hypertens. 1989; 2:2–8. [PubMed: 2643968]
11. Cochran RT Jr. Hyposthenuria in sickle cell states. Archives of Internal Medicine. 1963; 112:222–225. [PubMed: 14044821]
12. Oguanobi NI, Onwubere BJC, Ibegbulam OG, Ike SO, Anisiuba BC, Ejim EC, Agwu O. Arterial blood pressure in adult Nigerians with sickle cell anemia. Journal of Cardiology. 2010; 56:326–331. [PubMed: 20727714]
13. Brittain JE, Hulkower B, Jones SK, Strayhorn D, De Castro L, Telen MJ, Orringer EP, Hinderliter A, Ataga KI. Placenta growth factor in sickle cell disease: association with hemolysis and inflammation. Blood. 2010; 115:2014–2020. [PubMed: 20040765]
14. Teixeira PcGa, Cabral AnCV, Andrade SP, Reis ZSN, da Cruz LvPB, Pereira JB, de Barcelos Martins BO, de Lima Rezende CA. Placental Growth Factor (PlGF) Is a Surrogate Marker in Preeclamptic Hypertension. Hypertension in Pregnancy. 2008; 27:65–73. [PubMed: 18293205]
15. Morton J, Coles B, Wright K, Gallimore A, Morrow JD, Terry ES, Anning PB, Morgan BP, Dioszeghy V, KÃ¼hn H, Chaitidis P, Hobbs AJ, Jones SA, O'Donnell VB. Circulating neutrophils maintain physiological blood pressure by suppressing bacteria and IFNÎ^3-dependent iNOS expression in the vasculature of healthy mice. Blood. 2008; 111:5187–5194. [PubMed: 18281503]
16. Platt OS. Sickle cell anemia as an inflammatory disease. J Clin Invest. 2000; 106:337–338. [PubMed: 10930436]
17. Hebbel RP, Osarogiagbon R, Kaul D. The endothelial biology of sickle cell disease: inflammation and a chronic vasculopathy. Microcirculation. 2004; 11:129–151. [PubMed: 15280088]
18. Castro O, Brambilla DJ, Thorington B, Reindorf CA, Scott RB, Gillette P, Vera JC, Levy PS. The acute chest syndrome in sickle cell disease: incidence and risk factors. The Cooperative Study of Sickle Cell Disease. Blood. 1994; 84:643–649. [PubMed: 7517723]
19. Frenette PS. Sickle cell vasoocclusion: heterotypic, multicellular aggregations driven by leukocyte adhesion. Microcirculation. 2004; 11:167–177. [PubMed: 15280090]
20. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, Klug PP. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 1994; 330:1639–1644. [PubMed: 7993409]
21. Ataga KI, Brittain JE, Desai P, May R, Jones S, Delaney J, Strayhorn D, Hinderliter A, Key NS. Association of Coagulation Activation with Clinical Complications in Sickle Cell Disease. PLoS ONE. 7:e29786. [PubMed: 22253781]
22. Platt OS, Thorington BD, Brambilla DJ, Milner PF, Rosse WF, Vichinsky E, Kinney TR. Pain in Sickle Cell Disease. New England Journal of Medicine. 1991; 325:11–16. [PubMed: 1710777]
23. Vichinsky EP, Neumayr LD, Earles AN, Williams R, Lennette ET, Dean D, Nickerson B, Orringer E, McKie V, Bellevue R, Daeschner C, Manci EA. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. N Engl J Med. 2000; 342:1855–1865. [PubMed: 10861320]
24. Ataga KI, Moore CG, Jones S, Olajide O, Strayhorn D, Hinderliter A, Orringer EP. Pulmonary hypertension in patients with sickle cell disease: a longitudinal study. Br J Haematol. 2006; 134:109–115. [PubMed: 16803576]
25. Reinders A, Reggiori F, Shennan AH. Validation of the DINAMAP ProCare blood pressure device according to the international protocol in an adult population. Blood Pressure Monitoring. 2006; 11:293–296. 210.1097/1001.mbp.0000217998.0000296967.fb. [PubMed: 16932038]
26. de Greeff A, Reggiori F, Shennan AH. Clinical assessment of the DINAMAP ProCare monitor in an adult population according to the British Hypertension Society Protocol. Blood Pressure Monitoring. 2007; 12:51–55. [PubMed: 17303988]

27. Gaston M, Rosse WF. The cooperative study of sickle cell disease: review of study design and objectives. Am J Pediatr Hematol Oncol. 1982; 4:197–201. [PubMed: 7114401]

Table 1

Baseline Clinical and Laboratory Characteristics of Study Subjects

Characteristic	UNC (n=156)	CSSCD (n=1232)	p-value
Age[1] (years)	36 (27, 47)	27 (22.1, 32.7)	<0.0001
Age group(years)			
18–25	26 (17%)	508 (41%)	<0.0001
25–35	46 (29%)	489 (40%)	
35–45	39 (25%)	153 (12%)	
45–65	42 (27%)	81 (7%)	
≥ 65	3 (2%)	1 (0.8%)	
Genotype[2]			
SS	118 (76%)	833 (68%)	0.01
$S\beta^0$	10 (6%)	66 (5%)	
SD	1 (1%)	0 (0%)	
SC	18 (12%)	258 (21%)	
$S\beta^+$	9 (6%)	75 (6%)	
Female	97 (62%)	702 (57%)	0.2
Black	154 (99%)	1205 (98%)	0.9
Body mass index[1]	25.3 (21.9, 29.7)	20.9 (18.9, 23.7)	<0.0001
Tobacco use	47 (33%)	488 (40%)	0.1
Diagnosis of hypertension	32 (21%)	76 (6%)	<0.0001
Use of antihypertensive agent	38 (24%)	43 (5%)	<0.0001
History of stroke	14 (10%)	63 (5%)	0.03
History of acute chest syndrome	131 (84%)	742 (63%)	<0.0001
History of leg ulcers	33 (23%)	285 (24%)	0.9
White blood cell count ($\times 10^9$/L)[1]	9.5 (7.35, 11.45)	10.7 (8.4, 13.2)	<0.0001
Hemoglobin (g/dL)[1]	8.9 (7.7, 10.2)	9.1 (8.0, 11.0)	0.09
Platelet count ($\times 10^9$/L)[1]	413 (314, 504)	375 (287, 474)	0.005
Reticulocyte count (%)[1]	6.3 (4.5, 9.2)	7.9 (3.9, 12.9)	0.01
Fetal hemoglobin (%)[1]	5.9 (2.9, 11.8)	6 (3.3, 6.5)	0.8
Creatinine (mg/dL)[1]	0.7 (0.6, 0.91)	0.8 (0.6, 1.0)	0.3

[1] medians and interquartile ranges are provided for these variables

[2] For the CSSCD cohort, SS included SS and SS alpha thalassemia;

$S\beta^0$ included $S\beta^0$ thalassemia, $S\beta^0$ and alpha thalassemia, and $S\beta^0$ and delta thalassemia

Table 2

Association of Systolic and Diastolic Blood Pressure with Clinical Variables in UNC Cohort

Variable		N	Systolic Blood Pressure		Diastolic Blood Pressure	
			Median [IQR]	p value	Median [IQR]	p value
History of stroke	Yes	14	121 [118, 124]	0.8	75 [67, 78]	0.2
	No	128	123 [113, 133]		69 [64, 76]	
Smoking history †	Yes	47	120 [113, 134]	0.2	67 [59, 73]	0.01
	No	95	124 [116, 133]		71 [65, 78]	
Use of hydroxyurea	Yes	89	123 [114, 130]	0.3	69 [63, 76]	0.5
	No	67	124 [115, 136]		71 [64, 76]	
History of acute chest syndrome	Yes	131	123 [113, 133]	0.4	69 [64, 76]	0.9
	No	25	123 [117, 133]		71 [62, 77]	
History of hypertension	Yes	32	135 [124, 144]	<0.001	74 [63, 74]	0.03
	No	124	120 [113, 130]		69 [65, 84]	
History of retinopathy	Yes	100	123 [114, 131]	0.4	69 [63, 76]	0.1
	No	42	124 [116, 137]		72 [67, 78]	
Use of antihypertensive	Yes	38	131 [120, 144]	<0.001	74 [66, 83]	0.03
	No	118	121 [113, 129]		69 [62, 74]	
Mortality	Yes	21	123 [116, 133]	0.8	66 [64, 73]	0.5
	No	135	123 [114, 132]		70 [63, 76]	
Age *		156	ρ = 0.37	<0.0001	ρ = 0.26	0.001
Body Mass Index *		156	ρ = 0.41	<0.0001	ρ = 0.27	0.0006
Number of crisis in past year *		142	ρ = −0.16	0.06	ρ = 0.03	0.7
Tricuspid regurgitantjet velocity *		107	ρ = 0.07	0.5	ρ = 0.09	0.3

* Continuous variable and reported as Spearman correlations

† History of smoking included the smoking of cigarettes, cigars, or a pipe

IQR: Interquartile range

Table 3

Association of Systolic andDiastolic Blood Pressure with Laboratory Variables in UNC Cohort

Variable	N	Systolic Blood Pressure		Diastolic Blood Pressure	
		Spearman Correlation	p value	Spearman Correlation	p value
White blood cell count	156	−0.24	0.002	−0.14	0.07
Hemoglobin	156	0.18	0.02	0.20	0.009
Platelet count	155	−0.12	0.1	−0.17	0.04
Absolute neutrophil count	142	−0.24	0.004	−0.16	0.05
Absolute monocyte count	142	−0.18	0.03	−0.20	0.02
Reticulocyte count	155	−0.29	0.0003	−0.25	0.002
Fetal hemoglobin	153	−0.003	0.97	0.008	0.9
Lactate dehydrogenase	139	−0.19	0.02	−0.15	0.07
Total bilirubin	142	−0.29	0.0004	−0.27	0.001
Indirect bilirubin	139	−0.29	0.0006	−0.26	0.002
Placenta growth factor	39	−0.37	0.02	−0.10	0.5
Soluble fms-like tyrosine kinase-1	65	−0.07	0.6	0.23	0.06
Endothelin-1	28	0.18	0.4	0.24	0.2
Soluble vascular cell adhesion molecule	114	−0.15	0.1	−0.12	0.2
Urine protein/creatinineratio	66	0.17	0.2	−0.03	0.8
Creatinine	142	0.23	0.005	0.09	0.26