Inflammatory Cytokines are Associated to Lower Glomerular Filtration Rate in Patients with Hypertensive Emergency

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Research Article

Keywords: hypertensive crisis, estimated glomerular filtration rate (eGFR), Cytokines, Inflammation

Posted Date: May 5th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-463043/v1

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Inflammatory cytokines and hypertensive emergency

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Abstract

Introduction: Hypertension and kidney function are closely related. However, there are few studies on renal function during acute elevation of blood pressure (BP), denominated hypertensive crisis (HC). **Objectives**: To evaluate the relationship between renal function and inflammatory cytokines in HC, subdivided into hypertensive urgency (HUrg) and emergency (HEmerg). Methods: 74 normotensive subjects (NT), 74 controlled hypertensive (ContrHT), 50 patients with HUrg and 78 with HEmerg were studied. The glomerular filtration rate (eGFR) was estimated, and cytokine levels were measured. Statistical analysis was performed using the Kruskal-Wallis or Mann-Whitney test and Spearman's correlation, with significant differences p-value <0.05. **Results**: The eGFR was significantly lower in HEmerg group compared to the NT, ContrHT and HUrg groups. All cytokines were significantly elevated in patients with HC compared to the control groups (NT and ContrHT). In addition, the cytokines interleukin (IL)-1β, IL-6 and IL-10 were higher in the HEmerg group compared to the HUrg groups. There was a negative correlation between eGFR and the cytokines (IL-6, IL-8, IL-10 and TNF-α) in the HEmerg group. **Conclusions**: Elevated inflammatory cytokines are associated with reduced eGFR in individuals with HEmerg, indicating an involvement of the inflammatory process in the pathogenesis of acute elevations of BP.

Keywords: hypertensive crisis, estimated glomerular filtration rate (eGFR), Cytokines, Inflammation

Introduction

Hypertension is a growing world public health problem. High blood pressure may cause severe complications including coronary heart disease, stroke, heart failure, renal failure, and death unless it is diagnosed and treated early [1]. One acute consequence of inadequate blood pressure (BP) control is hypertensive crisis (HC), a serious clinical condition in which an abrupt increase in BP (systolic BP ≥180 mmHg and/or diastolic BP ≥120mmHg) can lead to acute lesions in target organs (heart, brain, kidneys, and arteries) promoting immediate or potential risk of death [2]. Hypertensive crisis is divided in an emergency (HEmerg), characterized by target organ damage (TOD) with immediate and potential risk of death or hypertensive urgency (HUrg), a situation without TOD and, consequently, no risk of potential death [3]. It is estimated that 1-2% of hypertensive individuals will have HC at some point in life [4].

The precise pathophysiology of the HC is poorly understood. However, two different but interrelated mechanisms may play central roles in its pathophysiology. The first is a failure in the autoregulation system of the vascular bed, which courses with a diminution of the perfusion pressure leading to a decrease in blood flow and an increase in vascular resistance, originating mechanical stress and endothelial injury [5]. The second mechanism is the activation of the renin–angiotensin system, leading to further vasoconstriction and thus generating a vicious cycle of injury and subsequently ischemia. Besides these mechanisms, a prothrombotic state may play a key role in HC [4,5].

On the other hand, the kidneys play an essential role in the regulation of BP with renal function acting a predictor of cardiovascular risk in hypertension. Chronic kidney disease and cardiovascular dysfunction may be causes and also consequences of persistent hypertension, resulting in a high risk of morbidity and mortality [6]. Considering that the renal system has an important participation in BP regulation, any type of renal artery disease or renal parenchymal disorder may cause HC [7]. Furthermore, acute kidney injury (AKI) may be a complication of hypertensive crisis [7,8]. In individuals with HEmerg complicated with AKI, the presence of subjacent renal disease at baseline and the phase of renal dysfunction at admission affect the rate of kidney recovery after improvement of the BP [7,9]. In addition, inflammatory cytokines participate in the pathogenesis of chronic hypertension by actions on renal blood flow and sodium balance [10,11]. Thus, there are few studies of the association between kidney function and the inflammatory process in cases of acute elevation of BP defined as HC. Therefore, this study will evaluate the influence of inflammatory markers on renal function in individuals suffering from acute elevations of BP.

Methods

This was a cross-sectional study conducted in patients treated in a tertiary referral

university hospital in the period from 2012-2014. This study was submitted to and approved by the Research Ethics Committee of Medical School at Sao Jose Rio Preto (FAMERP) according to national and international guidelines (number 3167/2005 – 05/16/2012). All participants signed informed consent forms. All methods were carried out in accordance with relevant guidelines and regulations. A total of 274 individuals aged 18 years and over were divided into four groups: Normotensive (NT; n = 74); Controlled Hypertensive (ContrHT; n = 74); Hypertensive Urgency (HUrg; n = 50); Hypertensive Emergency (HEmerg; n = 78). The control groups consisted of NT subjects selected in specialized outpatient clinics with BP <140 x 90 mmHg in the office without previous use of antihypertensive drugs and by controlled hypertensive individuals (ContrHT) being followed-up in the hypertension outpatient clinic with BP <130 x 80 mmHg measured by 24-hour ambulatory monitoring of blood pressure. The individuals with HC were recruited at the emergency room.

The criterium proposed by the Seventh Joint National Committee was used for the definition of HC [2]. HEmerg was characterized by severe elevations in BP complicated by evidence of impending or progressive TOD (hypertensive encephalopathy, hemorrhagic and ischemic strokes, acute myocardial infarction, acute pulmonary edema, unstable angina, acute aortic dissection and acute/progressive renal insufficiency). HUrg were situations associated with severe elevations in BP without TOD. The clinical history of all patients was taken, and they were submitted to physical examinations and diagnostic tests after signing an informed consent form previously approved by the Ethics Research Committee. In cases where patients were unable to sign, participation was authorized by parents or guardians.

To evaluate TOD better, patients in the HEmerg group were subdivided into two types of organic involvement: cerebrovascular (ischemic stroke, hemorrhagic stroke and hypertensive encephalopathy) and cardiovascular (acute pulmonary edema, acute myocardial infarction, unstable angina and acute aortic dissection).

The BP of patients was measured according to the recommended standard technique using a digital automatic sphygmomanometer (Omron Hem-711 DLX); the mean was calculated from at least three consecutive readings taken at one-minute intervals.

This study excluded female patients presenting with preeclampsia and eclampsia, and hypertensive patients with pseudocrises or chronic inflammatory diseases (rheumatoid arthritis, lupus, fibromyalgia, cancer and others). The clinical profile of the patients was obtained from electronic medical records.

Laboratory analyses

In order to measure inflammatory mediator levels, peripheral blood samples were collected in dry tubes and centrifuged at 3500 r.p.m. for ten minutes. The plasma was stored in

freezer tubes at -70°C. In the cases of the HEmerg and HUrg, blood samples were collected within four hours of emergency hospital admission. Interleukins (IL-1β, IL-6, IL-8 and IL-10) and tumor necrosis factor-alpha (TNF-α) were measured using MILLIPLEX® MAP kits and the enzyme-linked immunosorbent assay kit (ELISA) was used to measure interleukin 18 (IL-18). These specific cytokines for the present study were selected according to literature analyzes [11,12]. All cytokines were assayed in duplicate. Analyses of serum creatinine and potassium were performed using standard assays [12]. The estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI equation, developed by the Chronic Kidney Disease Epidemiology Collaboration [13].

Statistical analysis

This study was originally planned to test a difference of 10–20% in inflammatory cytokine levels with an alpha error of 5% and power of 85% giving a sample size of 80 patients per group. We did not reach this sample size but were still able to identify significant differences in biochemical parameters between the study groups.

The descriptive analyses of the variables are presented as median, minimum and maximum values. The Kruskal-Wallis, Mann-Whitney, chi-square and Fisher exact tests were used in the comparative study to analyze the epidemiological profile, metabolic factors and renal function. The eGFR, systolic BP (SBP), diastolic BP (DBP), creatinine and inflammatory cytokines were included in the Spearman correlation analysis. Outliers creatinine levels were identified and excluded using the GraphPad Prism. An alpha error of 5% was accepted; thus, statistical differences were considered significant when p-values were < 0.05.

Results

The characterization of the four study groups is shown in Table 1. BP and heart rate levels were significantly higher in the HUrg and HEmerg groups compared to the NT and ContrHT groups ($P < 0.0001$ for all). Moreover, the HUrg and HEmerg groups showed statistically higher levels of creatinine than the NT and ContrHT groups. Significantly lower levels of potassium were also found in the HEmerg group compared to the NT, ContrHT and HUrg groups ($P = 0.0118$, $P = 0.0366$ and $P = 0.036$, respectively). The eGFR was significantly lower in the HEmerg group compared to the NT, ContrHT e HUrg groups ($P < 0.0001$, $P = 0.0002$ and $P = 0.0345$, respectively).

The medications and the number of antihypertensive drugs used in the ContrHT, HUrg and HEmerg groups are shown in Table 2, which also shows the percentage of cardiovascular (acute pulmonary edema, acute myocardial infarction and unstable angina) and

cerebrovascular events (ischemic stroke, hemorrhagic stroke and hypertensive encephalopathy) in the HEmerg group. Normotensive patients did not use antihypertensive, antidiabetic or antilipemic drugs.

The biochemical profile, the BP, eGFR and age of patients in the cases of hypertensive emergency, subdivided in cerebrovascular and cardiovascular events, did not showed significant differences for the evaluated variables.

The figure 1 shows the inverse correlation between eGFR and age ($r = -0.54$; $P<0.0001$), SBP ($r = -0.30$; $P <0.0001$) and DBP ($r = -0.28$; $p <0.0001$). These correlations were made using the ContrHT, HUrg and HEmerg groups. Outliers creatinine levels were excluded for this analysis.

The Table 3 shows the results of the inflammatory cytokines for the four study groups. All proinflammatory cytokines were significantly higher in patients with HC, both HUrg and HEmerg, compared to the control groups (NT and ContrHT). Regarding IL-10, higher values were found in patients with HEmerg and HUrg compared to the NT and ContrHT groups ($p <0.0001$ for both). The cytokine levels were not significantly different between the HEmerg and HUrg groups except for IL-1β, IL-6 and IL-10.

The Table 4 shows the correlations between eGFR and inflammatory markers. There were negative correlations between eGFR and IL-1β ($r = -0,23$; $P = 0,0217$), IL-6 ($r = -0,30$; $P = 0,0037$), IL-8 ($r = -0.43$; $P <0.0001$), IL-10 ($r = -0.31$; $P = 0,0026$) and TNF-α ($r = -0.36$; $P = 0,0006$) in the HEmerg group. Furthermore, negative correlations were found between eGFR and IL-6 ($r = -0.34$; $P = 0.0098$) and TNF-α ($r = -0.29$; $P = 0.0231$) in the HUrg group.

Discussion

This study shows elevated levels of proinflammatory cytokines associated to reduced renal function in individuals suffering from acute hypertensive events. In spite of HC being an event common in the clinical emergency department [14-17], its pathophysiology continues unclear. Generally, this process is started by an imbalance between cardiac outcome and peripheral vascular resistance with participation of several mechanisms, including renal sodium handling, systemic vascular responses, cardiac output, and sympathetic outflow [4,5]. In addition, sudden increases in BP overlapping pre-existing hypertension appears to trigger deterioration of the kidney function [18].

In the present study, markers of renal function (creatinine and eGFR) were altered in individuals with HUrg and HEmerg. These two groups demonstrated upper creatinine levels and decrease in the eGFR compared to the control groups (NT and ContrHT), data confirmed by other studies investigating acute elevations of BP [18,19]. Moreover, HEmerg group evidenced declines in the eGFR compared to the HUrg group. As previously described, high

blood pressure and kidney function are deeply related and the association between them enhances cardiovascular risk; then increases in BP can be both a cause and a consequence of kidney disease. Lower kidney function may trigger HC, and HC can acutely injury the kidneys. Recently, a study evaluated individuals with HC and showed that plasma renin and aldosterone were increased, suggesting neurohormonally mediated vascular injury and kidney dysfunction [20]. Additionally, to neurohormonal imbalance in HC, kidney injury results from changes in renal vascular self-regulation. In physiological conditions, when kidney perfusion pressure reduces and renal blood flow is decreased, vascular resistance lowers through self-regulation mechanism. However, in HC, this regulatory mechanism is impaired. Other mechanisms for vascular injury and kidney dysfunction include immunity-mediated and inflammatory fibrosis. Animal models have been used to evidence the role of inflammatory process and stress in high blood pressure-mediated vascular and kidney damage [5, 20].

In this study, creatinine levels varied greatly in the HUrg and HEmerg groups, but not in the ContrHT group. Hence, similar to another study it was not possible to discover whether the renal dysfunction was due to pre-existing chronic kidney disease or acute kidney failure as a manifestation of the HC [21]. Anyway, one third of hospitalized patients with acute elevations of BP course with >25% reductions in renal function and are at a higher cardiovascular risk [9]; renal dysfunction is an independent predictor of mortality among patients with HC [22]. Moreover, the risk of developing end-stage renal disease in patients with malignant hypertension, one type of HEmerg, is markedly elevated [23]. The major determinants of long-term renal failure in cases of malignant hypertension are initial serum creatinine values and BP control. Although the current study was not longitudinal, creatinine and BP also correlated negatively to eGFR. Acute kidney disease caused by malignant hypertension may also reflect difficulty over the long term to regulate BP in hypertensive individuals, a fact observed in this study. The majority of individuals who developed HEmerg took more than three antihypertensive drugs. Moreover, patients with HEmerg were older than the individuals in the other groups as reported in other studies [14,15]. Thus, the greater number of older patients with HEmerg shows that the incidence of cardiovascular disease, especially in men, rises almost linearly with increasing age [24].

Hence, HEmerg comprise a group of more severely ill subjects, with a higher prevalence of difficult-to-control hypertension and a greater propensity to develop cerebrovascular and renal complications.

In this study, we observed the presence of a greater inflammatory process in cases of HC. All proinflammatory cytokines were elevated in patients with acute elevations in BP in both the HUrg and HEmerg groups compared to control subjects (NT and ContrHT). Only the IL-1B, IL-6 and IL-10 cytokines were significantly higher in the HEmerg group compared to the HUrg group. Unlike the other cytokines, IL-10 limits the severity of hypertension by inhibiting

the activation of nuclear factor-kappa beta (NFkB) and limiting the production of proinflammatory cytokines and chemokines during hypertension [25,26]. Thus, it is interesting to reemphasize that in our study, the HEmerg group presented significantly greater levels of IL-10 than the other three groups, including the HUrg group, a fact that possibly shows a greater compensatory response in more severe cases. Therefore, in the current work, acute elevations of BP course with worse inflammation than in chronic hypertension from the point of view of the activation of both pro-inflammatory and anti-inflammatory markers.

Recent studies have reported that cells of the immune system (both innate and adaptive immunity) contribute to the pathogenesis of chronic hypertension via their actions in the kidney, the vasculature and the brain. Inflammatory cytokines contribute to the pathogenesis of hypertension through effects on renal blood flow and sodium handling by modulating functions of the epithelial cells and vasculature in the kidneys. In animal models, the administration of angiotensin II followed by exposure to a high-salt diet results in hypertension, cortical vasoconstriction, and increase in renal accumulation of macrophages and lymphocytes [27,28]. Inflammatory cells are present in the kidneys of patients with severe hypertension as demonstrated in autopsy studies [29] and animal models have demonstrated that myeloid cells and lymphocytes make distinct contributions to the pathogenesis of hypertension. Circulating monocytes and tissue macrophages (myeloid cell populations) from the innate immune system exacerbate both elevations in BP and TOD in hypertension thereby promoting endothelial dysfunction and provoking sodium retention in the kidney by disrupting renal blood flow [28,30,31]. On the other hand, T- lymphocytes can directly regulate the BP inducing hypertension through vascular dysfunction [32,33], while B-lymphocytes can alter BP indirectly by facilitating T-cell activation and consequent cytokine generation [34-36] with both these conditions being generated by the adaptive immune system. In turn, cytokines can modulate the salt-water balance by altering sympathetic tone and renal nerve activity, by provoking endothelial dysfunction with secondary effects on renal blood flow, and/or by augmenting sodium transport in the nephron [37], mechanisms involved in the pathophysiology of HC.

Some studies have shown that inflammation markers and oxidative stress are elevated in patients with chronic kidney disease and the present study shows an association between inflammatory markers and reduced renal function in cases of HEmerg [11,38]. Similarly, inflammatory cytokines are predictors of the initiation and progression of diabetic kidney disease, regulating the immune response and exerting important actions as effectors of lesions, including the development of nephropathy [39]**.** In the present work, all the cytokines were higher in the HC group compared to control groups. In general, cytokines are capable of regulating the synthesis of other pro-inflammatory molecules and, consequently, active several inflammatory pathways and

generate vascular damage. Thus, IL18 is capable of regulating the synthesis of IL1 and TNF-α, and interferon (IFN) G [40], in turn increasing chemokine receptors in mesangial renal cells [41]. Furthermore, IL8 increases the expression of intercellular adhesion molecule 1 (ICAM-1) [42] and promotes endothelial cell apoptosis [43]. Interestingly, the elevated expression of ICAM-1 was observed in cases of the hypertensive emergencies [44].

This study has both strengths and limitations. Its strengths include the contribution of clinically relevant and previously unavailable data on the association between renal function and the inflammatory process in patients suffering from HC. The numbers of individuals evaluated in the four groups of this study are higher than in other published studies, which gives consistency to the results obtained. In addition, the evaluation of different inflammatory cytokines and the inclusion of two control groups (NT and ContrHT) provide results that are more robust.

However, some limitations should be considered. First, this is a cross-sectional study, so the data do not allow the identification of cause-and-effect relationships. Second, the sample size of the HUrg group was smaller than the other groups because this study was performed in a tertiary referral hospital with a high number of complex cases, which made it difficult to enroll patients with HUrg. However, it was still possible to identify a significant difference in variables. Finally, more specific markers of renal function, such as cystatin C and neutrophil gelatinase associated lipocalin (NGAL), were not used.

To the best of our knowledge, this is the first study performed in individuals with HC associating renal function with inflammatory cytokines. Elevation of proinflammatory (IL-1β, IL-6, IL-8, IL-18 and TNF-α) and anti-inflammatory cytokines (IL-10) appear to participate in the pathophysiology of reduced renal function in cases of elevated BP, especially in patients with HEmerg. The results of this study should encourage further investigations to better characterize the role of the inflammatory process in the pathogenesis of HC.

Acknowledgments

The authors thank the reviewer for correcting both spelling and grammar of the English text. JFV-M designed the study. DOA, FLA, ALPM, FMV, DRSS, VSL, LBF, MFG, JCY-T, LNC-M, and JFV-M contributed equally to the literature review, data interpretation, creation of figures, and the writing of the manuscript. All authors read and approved the final draft.

Funding

The authors thank FAPESP for the grant support (2013/09868-3).

Declaration of interest

The authors declare no conflict of interest.

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Table 1. Sociodemographic data, metabolic profile and personal history of normotensive (NT), controlled hypertensive (ContrHT), hypertensive urgency (HUrg) and hypertensive emergency (HEmerg) individuals.

Variable	**NT (a) (n = 74)**		**ContrHT (b) (n = 74)**		**HUrg(c) (n = 50)**		**HEmerg(d) (n = 78)**		**P-value***					
Gender	**N(%)**		**N(%)**		**N(%)**		**N(%)**							
Female	50(71)		52(70)		23(46)		38(49)							
Ethnical background									**a x b**	**a x c**	**a x d**	**b x c**	**b x d**	**c x d**
White	69(93.2)		63(85.1)		39(78)		65(83.3)							
Non-White	5(6.8)		11(14.9)		11(12)		13(16.7)							
	Median	**Range**	**Median**	**Range**	**Median**	**Range**	**Median**	**Range**						
Age (years)	53.5	37-83	61	25-84	58	32-92	64.5	25-97	**0.0008**	0.0539	**<0.0001**	0.3291	0.059	**0.0264**
BMI (kg/m²)	26.8	18.9-36.9	29.7	21-47.9	29.3	19.4-47.4	25.9	17.5-46.8	**0.0003**	0.0822	0.9227	0.3121	**0.0005**	0.1724
SBP (mmHg)	117	95-133	113.5	93-130	200	160-300	196.5	124-300	0.2183	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	0.8318
DBP (mmHg)	75	55-94	71	50-88	120	110-180	120	110-240	**0.0007**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	0.8956
HR (bpm/min)	68	55-90	71	42-108	81	55-150	87	53-141	0.1446	**<0.0001**	**<0.0001**	**<0.000**	**<0.0001**	0.2097
Biochemistry														
Creatinine (mg/dL)	0.8	0.5-1.3	0.9	0.6-1.7	1.0	0.6-10.3	1.0	0.5-8.1	0.1284	**0.0003**	**<0.0001**	**0.0165**	**<0.0001**	0.3723
Potassium (meq/L)	4.5	3.0-5.3	4.4	3.4-5.8	4.4	3.5-7.7	4.2	2.9-8.0	0.2209	0.9859	**0.0118**	0.4407	**0.0366**	**0.036**
eGFR(mL/min/1.73m²)														
CKD-EPI	88	48-128	82	35-129	76	9-123	66	8-125	**0.0339**	**0.0084**	**<0.0001**	0.3492	**0.0002**	**0.0345**
Personal history			**n (%)**		**n (%)**		**n (%)**							
Known hypertension			74(100)		49(98)		72(92.3)					0.4032	**0.0166**	0.2453
Dyslipidemia			50(67.5)		19(38)		45(57.6)					**0.0013**	0.2149	**0.0319**
Diabetes mellitus			33(44.5)		4(8)		13(16.6)					**<0.0001**	**0.0002**	0.1682

Kruskal-Wallis, Mann-Whitney and Fisher exact test; BMI = Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; EGFR: Glomerular filtration rate; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration.

Table 2: Distribution of controlled hypertensive individuals (ContrHT), hypertensive urgency (HUrg) and hypertensive emergency (HEmerg) according to the use of medications.

Variable	ContrHT (a) (n = 74)	HUrg (b) (n = 50)	HEmerg (c) (n = 78)	P-value*		
Anti-hypertensive drugs	**n (%)**	**n (%)**	**n (%)**	**a x b**	**a x c**	**b x c**
Diuretics	62(83.7)	26(52)	44(56.4)	**0.0002**	**0.0004**	0.7165
β blockers	22(29.7)	33(66)	41(52.5)	**<0.0001**	**0.0052**	0.1465
BCC	23(31)	16(32)	26(33.3)	>0.9999	0.8625	>0.9999
SRA blockers (ARB & ACEI)	59(79.7)	44(88)	74(94.8)	0.3293	**0.0062**	0.1872
Others	7(9.4)	12(24)	28(35.8)	**0.0407**	**0.0001**	0.1759
Antilipemic						
Statins	49(66.2)	19(38)	44(56.4)	**0.0031**	0.2457	**0.0479**
Fibrates	1(1.3)	-	1(1.2)	>0.9999	>0.9999	>0.9999
Antidiabetic drugs						
Oralantidiabetic drugs	33(44.5)	4(8)	11(14.1)	**<0.0001**	**<0.0001**	0.4018
Insulin	6(8.1)	1(2)	4(5.1)	0.2399	0.5305	0.6474
Antiaggregant drugs	26(35.1)	21(42)	51(65.3)	0.4566	**0.0003**	**0.011**
Anticoagulant	1(1.3)	4(8)	7(8.9)	0.1566	0.0639	>0.9999
1 anti-hypertensive drug	8(10.8)	5(10)	4(5.1)	0.9012	0.213	0.3215
2anti-hypertensive drugs	29(39.1)	16(32)	21(26.9)	0.4233	0.1126	0.5423
3anti-hypertensive drugs	25(33.7)	16(32)	24(30.7)	0.8422	0.6953	0.8818
>3anti-hypertensive drugs	9(12.1)	11(22)	27(34.6)	0.158	**0.0012**	0.1325
Target organ damage Acute pulmonary edema			24(30.8)			
Ischemic stroke			24(30.8)			
Hemorrhagic stroke			13(16.6)			
AMI			6(7.7)			
Unstable Angina			6(7.7)			
Hypertensive encephalopathy			5(6.4)			

Kruskal-Wallis and Mann-Whitney tests; AMI: Acute myocardial infarction; NT:Normotensive; ContrHT: Controlled hypertensive; HUrg: hypertensive urgency; HEmerg: hypertensive emergency.

Table 3: Measurement of inflammatory cytokine levels in normotensive (NT), controlled hypertensive (ContrHT), hypertensive urgency (HUrg) and hypertensive emergency (HEmerg) subjects.

Variable	**NT (a) (n = 74)**		**ContrHT(b) (n = 74)**		HUrg**(c) (n =50)**		HEmerg**(d) (n = 78)**		**P-value***					
	Median	**Range**	**Median**	**Range**	**Median**	**Range**	**Median**	**Range**	**a x b**	**a x c**	**a x d**	**b x c**	**b x d**	**c x d**
IL-1β(pg/mL)	0.07	0.00-5.54	0.05	0.00-14.4	0.10	0.02-24.8	0.3	0.14-81.3	0.2288	0.0652	**<0.0001#**	**0.0049***	**<0.0001#**	**<0.0001#**
IL-6(pg/mL)	0.63	0.00-51.5	0.67	0.00-22.6	4.45	0.27-48.6	7.45	0.51-386	0.9038	**<0.0001#**	**<0.0001#**	**<0.0001#**	**<0.0001#**	**0.0332***
IL-8(pg/mL)	11.4	1.07-63.7	9.7	2.7-49.9	21.3	1.61-1174	21.7	4.03-5034	0.1714	**<0.0001#**	**<0.0001#**	**<0.0001#**	**<0.0001#**	0.963
IL-10(pg/mL)	2.28	0.82-37.9	1.15	0.07-158	4.19	0.32-335	6.3	0.36-213	**<0.0001#**	**<0.0001#**	**<0.0001#**	**<0.0001#**	**<0.0001#**	**0.0384***
IL-18(pg/mL)	16.95	0.3-93.7	10.3	1.17-210.7	22.05	4.1-129.5	20.1	1.13-80.5	**0.0022***	**0.0079***	**0.004***	**<0.0001#**	**<0.0001#**	0.8732
TNF-α(pg/mL)	14.27	2.32-32.6	12.42	2.47-25	20.8	9.3-101	20.3	2.6-264	0.0901	**<0.0001#**	**<0.0001#**	**<0.0001#**	**<0.0001#**	0.3547

*: P-value <0.05; #: P-value <0.001;Tests used: Kruskal Wallis and Mann-Whitney; IL-1 β: Interleukin 1β; IL-6: Interleukin 6; IL-8:Interleukin 8; IL-10:Interleukin 10; IL-18:Interleucina18; TNF-α:Tumor necrosis factor-α.

Table 4: Correlation between glomerular filtration rate (eGFR) and inflammatory markers.

eGFR (CKD-EPI)	NT	ContrHT	HUrg	HEmerg
IL-1β	0.17	0.06	-0.05	**-0.23***
IL-6	-0.03	0.10	**-0.34***	**-0.30***
IL-8	-0.19	-0.13	0.17	**-0.43***
IL-10	-0.008	-0.09	-0.06	**-0.31***
IL-18	**0.26***	0.09	0.13	0.008
TNF-α	0.03	-0.16	**-0.29***	**-0.25***

Correlation coefficient (r) *: P-value < 0.05 Spearman correlation; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; NT: Normotensive; ContrHT: Controlled hypertensive; HUrg: Hypertensive urgency; HEmerg: Hypertensive emergency; IL-1 β: Interleukin 1β; IL-6: Interleukin 6; IL-8: Interleukin 8; IL-10: Interleukin 10; IL-18: Interleukin 18; TNF-α: Tumor necrosis factor-α.

Figure 1: Spearman correlation of glomerular filtration rate (eGFR) with systolic blood pressure (SBP), diastolic blood pressure (DBP), age and creatinine considering controlled hypertensive, hypertensive urgency and hypertensive emergency subjects. Outliers creatinine levels were excluded by the GraphPad Prism.

igure 1

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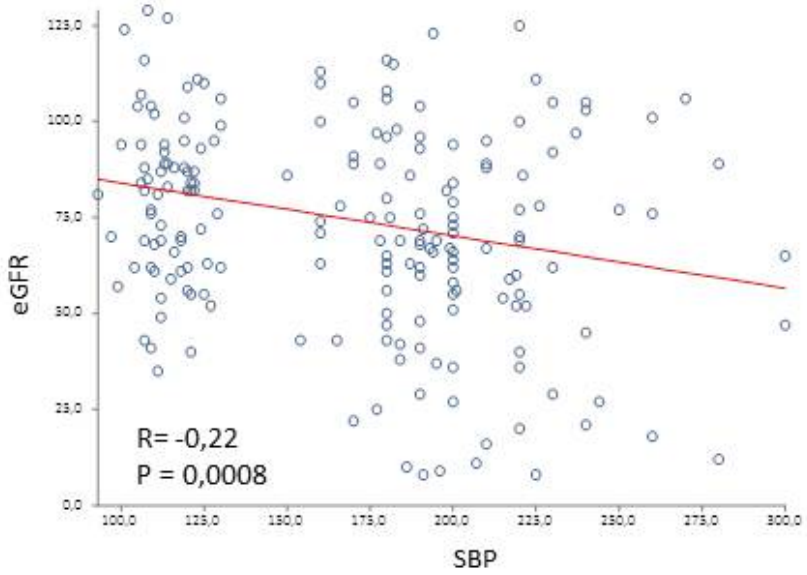
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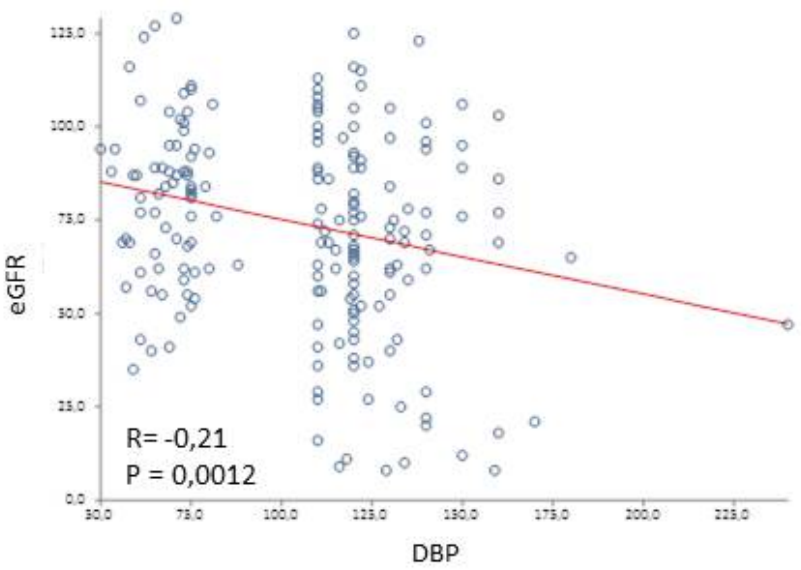
P = 0,0008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DBP
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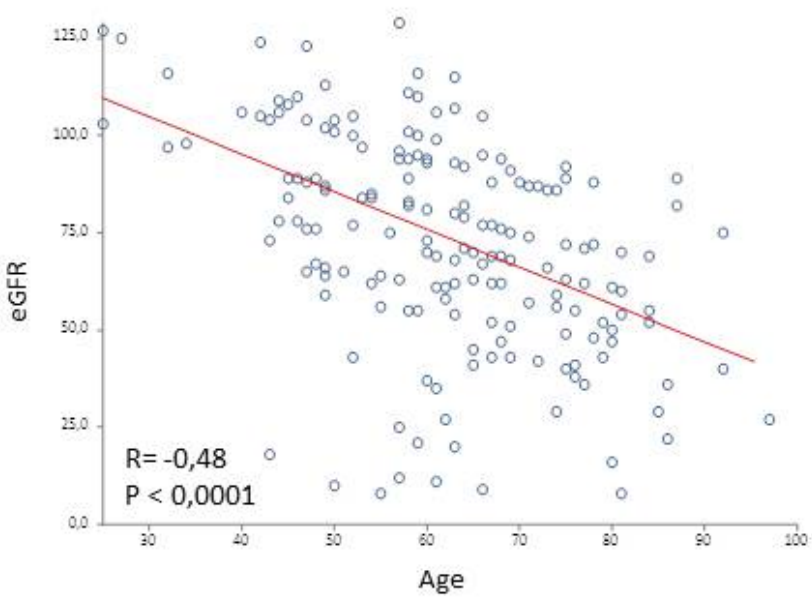
P = 0,0012


eGFR
Age
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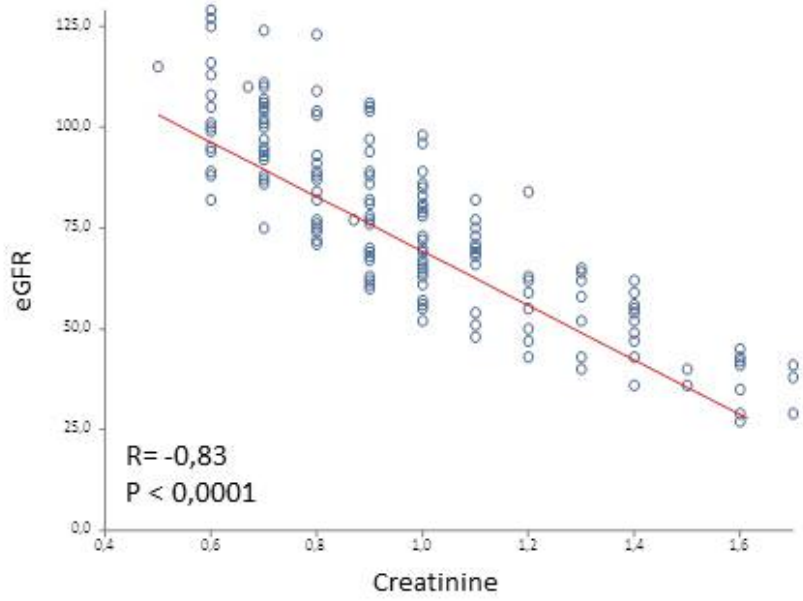
P < 0,0001


eGFR
Creatinine
R= -0,83
P < 0,0001

Figures

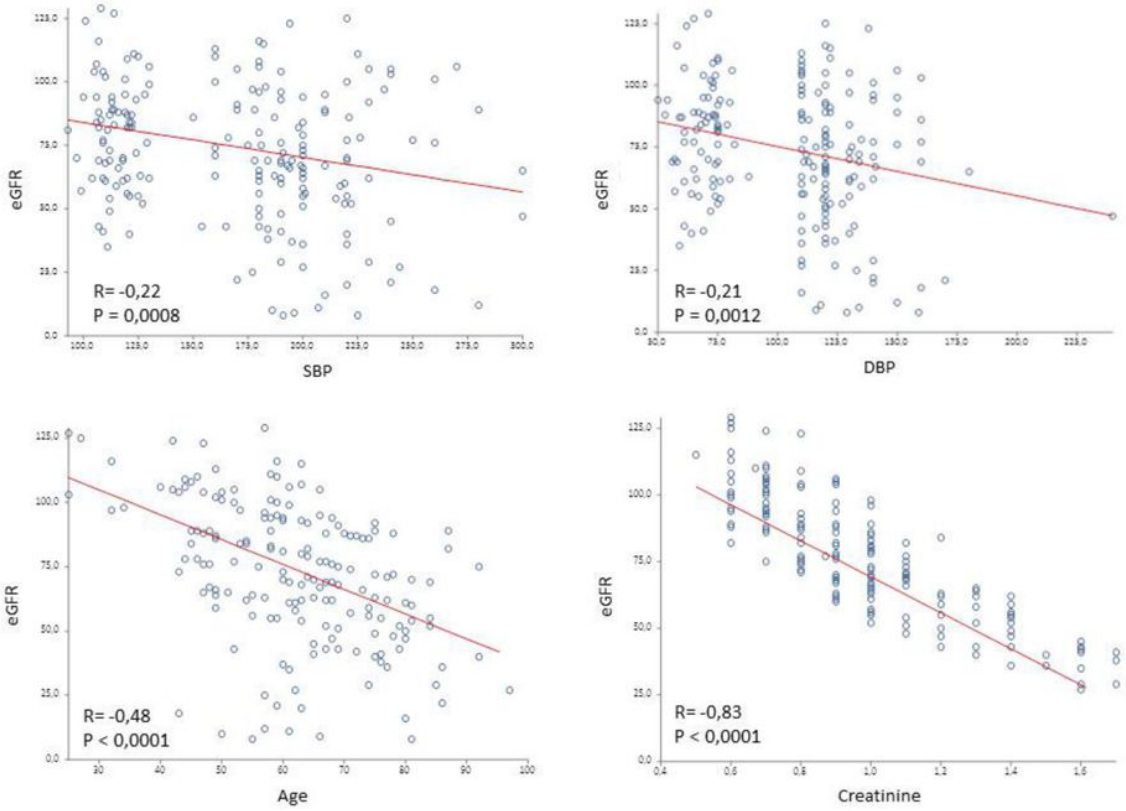


Figure 1

Spearman correlation of glomerular filtration rate (eGFR) with systolic blood pressure (SBP), diastolic blood pressure (DBP), age and creatinine considering controlled hypertensive, hypertensive urgency and hypertensive emergency subjects. Outliers creatinine levels were excluded by the GraphPad Prism.