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Assessing the variability and the role of inflammatory cytokines and monocyte chemoattractant protein-1 (MCP-1) in predicting stroke among hypertensives: A case-control study

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ABSTRACT

Background: Atherosclerosis is a complex lipid-driven inflammatory disease in which numerous cell types and inflammatory mediators are involved in the progression of hypertension to stroke. Mediators' markers that could predict the progression of hypertension to stroke are of research importance. We assessed the predictive value of individual and combined cytokines and monocyte chemoattractant protein-1 (MCP-1) among hypertensives with or without stroke.
Methods: In a case-control study, we enrolled 63 cases with stroke and hypertension (HPT-S), 59 stroke-free hypertensives (HPT), and 53 stroke free normotensives as controls (CS). Sociodemographic data and blood samples were collected for the estimation of Interleukin-10 (IL-10), IL-6, IL-8, IL-1β and monocyte chemoattractant protein-1 (MCP-1) using commercially available ELISA kits from Biobase Biotech, Shanghai, China. The Receiver Operator Characteristics (ROC) analysis was used to calculate diagnostic accuracy for cytokines in predicting stroke among hypertensives. A combined bioscore model of IL-10 and MCP-1 was generated to predict stroke among hypertensives. The multiple logistic regression analysis was used to assess the chances of IL-10 and MCP-1 in predicting stroke among hypertensives. Statistical analyses were performed using R-language.
Results: The HPT-S group had significantly higher levels of MCP-1 and IL-10 compared to the HPT and CS groups ($p < 0.05$). There was no significant difference in IL-1β, IL-8 and IL-6 amongst the three study groups. MCP-1 and IL-10 were predictive of stroke occurrence among hypertensives and were used to develop a bioscore model. An elevated MCP-1 and IL-10 with a bioscore 2 had a predictive accuracy of 0.81, a sensitivity of 0.77 and specificity of 0.84. At a bioscore of 1, the sensitivity and specificity for predicting stroke among hypertensives was 97.0% and 61.0% respectively. In a binary logistic regression, having a bioscore of 1 [aOR = 20.43, 95% CI (2.17–192.62), $p = 0.008$] or 2 [aOR = 26.00, 95% CI (2.92–231.31), $p = 0.003$] were significantly associated with stroke occurrence among hypertensives.
Conclusion: Higher levels of IL-10 with a concomitant level of MCP-1 could serve as a good predictor of stroke among hypertensives. Subsequently, MCP-1 may prove useful as a therapeutic target for atherosclerosis in hypertensives. Combined bioscore of MCP-1 and IL-10 could serve as a good predictor of stroke among hypertensives.

Abbreviations: HPT-S, Hypertension with stroke; HPT, Stroke-free hypertensives; CS, Controls; IL-10, Interleukin-10; MCP-1, monocyte chemoattractant protein-1; CT, Computed tomography; MRI, Magnetic resonance imaging; ELISA, Enzyme-linked immunosorbent assay; EDTA, Ethylene diamine tetracetic acid; SBP, Systolic blood pressure; DBP, Diastolic blood pressure.

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1. Introduction

Cardiovascular diseases (CVDs), including hypertension and stroke are among the leading causes of death worldwide, and responsible for the majority of disabilities [1,2]. Stroke incidence shows substantial disparities over time [3] and in geographic distribution [4]. Recent trends suggest that Sub-Saharan Africa now bears the highest burden of stroke with age-standardized stroke incidence rates of up to 316 per 100 000, prevalence rates of up to 14 per 1000 population and 1-month fatality rates of up to 40% [5,6]. Stroke among young adults has devastating consequences because of the longer-lasting impact of stroke-related disability on quality of life and productivity [7].

The diagnosis of arterial stroke differentiates ischemia from hemorrhage. Arterial stroke may be due to arterial occlusion or stenosis, while ischemia stroke is attributed to leakage or rupture of an artery [8]. The most prevalent infections following a stroke are pneumonia and urinary tract infections. In addition to lengthening hospital stays, post-stroke infections are a major factor in both short- and long-term mortality and morbidity [9]. Post-stroke infections and other complications are commonly attributed to neurological sequelae such as immobilization due to motor paralysis or dysphagia as a risk of aspiration [9,10].

The increased prevalence of modifiable and non-modifiable cardiovascular risk factors and the ageing of populations have resulted in stroke becoming a major healthcare problem in low and middle-income countries. Dyslipidemia, obesity, insulin resistance and certain lifestyle are risk factors of hypertension associated with increase rate of cardiovascular events such as stroke [11]. Hypertension has also been established as an independent risk factor for cardiovascular diseases including acute myocardial infarction, stroke, and coronary artery disease [12]. It has also been linked with endothelial cell injury and increased permeability of arterial walls to lipoproteins culminating in vascular atherosclerosis [13].

Atherosclerosis is a complex lipid-driven inflammatory disease in which numerous cell types and inflammatory mediators are involved [14]. The initiating step in atherogenesis is endothelial dysfunction, which can be induced by oxidative injury like dyslipidemia or hypertension [15]. Subsequently, chronic activation of inflammation significantly influence the advancement of stroke, thereby modifying the course of the acute phase of stroke [16].

An increase in the production of pro-inflammatory cytokines and a decrease in production of anti-inflammatory cytokines is associated with a larger infarct size in animal models and a worse clinical outcome [17]. Tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), interleukin (IL)-1β, IL-6, and IL-10 are inflammatory cytokines found to be related to ischemic stroke and are being considered as therapeutic targets and biomarkers for prognosis. MCP-1 plays a crucial role in initiating atherosclerosis by recruiting macrophages and monocytes to the vessel wall. Studies have found higher levels of MCP-1 to be related to increased risk of stroke, suggesting that MCP-1 signaling pathway could be a therapeutic target to lower stroke risk [18]. Again, in a large population-based sample and community studies, levels of MCP-1 are correlated with atherosclerotic risk, suggesting that MCP-1 could be a therapeutic target for atherosclerosis [19,20]. However, the predictive capacity of IL-10 in predicting stroke among hypertensives is warranted as no prior study has investigates IL-10 as a marker of stroke among hypertensive.

Lipid accumulation into the arterial wall promotes inflammation that involves the local and systemic activation of innate and adaptive immune response [21]. The inflammatory responses to ischemia changes with time, knowing when these cytokines are increased or decreased and how they affect infarct volume is important in understanding their clinical utilization. The role of IL-10 in hypertension and stroke has been investigated in both human studies and animal models [22,23]. The neuroprotective role of IL-10 in ischemic stroke has been confirmed in animal studies by the fact that administration of exogenous IL-10 and the upregulation of IL-10 decreases infarct size in rats after permanent focal ischemia [24]. In clinical studies, lower IL-10 serum levels have been associated with increased risk of stroke [25]. IL-10 upregulation has been reported in post ischemic stroke through the activation of ischemic and contralesional neurons resulting in the loss of inflammation during hypertension and stroke [26,27]. This has highlighted endogenous IL-10 as a potential therapeutic target to reduce inflammation and ischemic damage particularly under hypertension [28]. Although studies have investigated IL-10 as a marker of clinical outcomes in stroke (such as post stroke depression and death) [29,30], the use of IL-10 as a predictive marker of stroke among hypertensives has not received great attention.

Inflammatory response to stroke is extremely complex, with multiphasic pro- and anti-inflammatory responses. The levels inflammatory cytokines and MCP-1 had been correlated with disease outcome in stroke with focusing on the predictive role of the marker as hypertension progresses to stroke. We assessed the predictive value of individual and combined cytokines and MCP-1 among hypertensives with or without stroke. Determination and profiling of cytokine levels and their diagnostic accuracies in hypertensives before the onset of stroke would contribute to understanding their role in monitoring the progression of hypertension to stroke.

2. Materials and methods

2.1. Study design and site

This hospital-based case-control study was conducted at the Department of Medicine, Komfo Anokye Teaching Hospital (KATH), in the Ashanti Region of Ghana. KATH is the second largest tertiary hospital in Ghana with a thousand-bed capacity and a major referral centre.

2.2. Sampling of study population

A non-proportional randomized sampling technique was used to recruit 175 participants, aged 18 years and above, comprising 53 normotensives with no other chronic condition, and 122 hypertensives as cases [(59 without stroke (HPT) and 63 with stroke (HPT-S)]. Inclusion criteria for each case group included patients presenting with hypertension (defined as BP $\geq$ 140/90mmHg) and controls with normal blood pressure (defined as BP of and below 130/80 mmHg). Stroke was diagnosed with CT scan and Echocardiogram. Normotensives with overt and medical records of cardiovascular diseases, cancer, hepatic and lung diseases, chronic renal disease and rheumatoid arthritis were excluded from the study.

2.3. Ethical considerations

This study was approved by the Committee of Human Research Publications and Ethics of the Kwame Nkrumah University of Science and Technology and Komfo Anokye Teaching hospital. Written informed consent was also sought from study participants where they were adequately informed of the procedures, nature, risk, and the purpose of the study according to the Helsinki declaration [31].

2.4. Questionnaire administration

A detailed self-designed semi-structured questionnaire was administered to each consented participant to obtain their socio-demographic characteristics such as age, gender, educational level, marital status, smoking, alcohol consumption and exercise level. Blood pressure was measured using an automated sphygmomanometer (Intelli Sensetm boots blood Pressure monitor, London), at the right arm after individuals have had a rested period. The blood pressure were measured in the morning before their medication.

2.5. Diagnosis and definitions

Hypertension was diagnosed using WHO definition as a systolic blood pressure (SBP) of 140 mm Hg or more, or a diastolic blood pressure (DBP) of 90 mm Hg or more or on antihypertensive drug. Normotensives were participants with systolic blood pressure (SBP) of 120 mm Hg or less, or a diastolic blood pressure (DBP) of 80 mm Hg or less.

Stroke was diagnosed with Cranial CT or MRI, performed within 10 days of symptom onset. The type of stroke classification was based on clinical evaluation and brain neuroimaging (CT or MRI of the brain). All the patients recruited had ischemic stroke caused by deficient blood and oxygen supply to the brain. Ischemic stroke was typed clinically using the presumed etiological sub-types as defined using the Trial of Org 10172 in Acute Stroke Treatment criteria [32].

Controls were consenting stroke and hypertension-free adults, mostly from the communities in the areas of the hospitals where cases were recruited from. Stroke-free status was confirmed with the 8-item questionnaire for verifying stroke-free status (QVSFS) which has 98% negative predictive value [33]. Controls were matched by age (+/− 5 years), sex and ethnicity.

In this study, Body mass index (BMI) was used to diagnose those who are at least overweight (i.e., BMI > 24.9 kg/m2). Exercise was defined as any activity causing light perspiration or a slight to moderate increase in breathing or heart rate for at least 30 minutes. Alcohol intake was defined as the intake of at least one bottle of an alcoholic beverage per day. Participants were classified as smokers based on whether the respondent is in the habit of smoking at least one cigarette a day.

2.6. Blood sample collection and laboratory analysis

About 5 ml venous blood was collected from all study participants by venipuncture, under quality control and safety procedures. Thereafter, 3 ml was placed in a serum gel separator tube and the rest of the 2 ml into sterile Ethylene Diamine Tetracetic Acid (EDTA) tube. The serum gel separator tube sample was processed by centrifugation at 3000 rpm for 10 minutes (20°C) and the serum collected into fresh cryovials tube and stored at −80°C until further analysis. The obtained sera were used for the determination of immunological markers including MCP-1, IL-1β, IL-4, IL-6 and IL-10 levels using ELISA kits obtained from Biobase Biotech, Shanghai, China. The protocols for determining the concentrations of these immunological markers were followed and measured spectrophotometrically, using an, ELISA microplate analyzer (inqaba biotec, UK, model no.: RT0400814GDM). The EDTA sample was used for the haematological analysis using an automated haematological analyzer (Sysmex Automated Hematology Analyzer, Kobe, Japan, XP-300, model no.: AC580857).

2.7. Statistical analysis

Statistical analyses were performed using SPSS version 26.0 and R language version 4.0.2. The distribution of continuous variable was determined by the Shapiro-Wilk test for normality. Continuous variables were presented as means with standard deviations for parametric variables or medians with interquartile ranges for non-parametric variables. Categorical variables were presented as frequencies and percentages. Association between study groups were performed using the Chi-Square or the Fischer's Exact test. Comparisons of cytokines amongst the three groups were performed using the Kruskal Wallis test, followed by the Dunnet C multiple comparison test. Receiver Operator Characteristics (ROC) analysis from the plotROC package in R [34], was used to determine the diagnostic accuracy for cytokines in predicting stroke among hypertensives. A combined bioscore model of IL-10 and MCP-1 was generated to predict stroke among hypertensives. In the bioscore model, having higher levels of IL-10 (above the cutoff) were given a bioscore of 1, whilst lower levels of IL-10

Table 1
Socio-demographic and clinical characteristics of study participants.

Variable	Control (n = 53)	Cases (n = 122)	*p*-value	HPT (n = 59)	HPT-S (n = 63)	*p*-value
Gender			0.404			0.069
Male	31(58.5)	63(51.6)		25(42.4%)	38(60.3%)	
Female	22(41.5)	59(48.4)		34(57.6%)	25(39.7%)	
Educational level			<0.001[¥]			0.505
None		25(20.5)		11(18.6%)	14(22.2%)	
Primary	3(5.7)	30(24.6)		13(22.0%)	17(27.0%)	
JHS	6(11.3)	11(9.0)		8(13.6%)	3(4.8%)	
SHS	4(7.5)	42(34.4)		21(35.6%)	21(33.3%)	
Tertiary	40(75.5)	14(11.5)		6(10.2%)	8(12.7%)	
Occupational status			0.007[¥]			0.014 [ζ]
Unemployed	16(30.2)	67(54.9)		28(47.4%)	35(55.6%)	
Formally employed	8(15.1)	39(32.0)		2(3.4%)	10(15.9%)	
Self/Informally employed	29(54.7)	16(13.1)		29(49.2%)	18(28.6%)	
Smoke			0.128			
Yes	1(1.9)	0(0.0)		0(0.0)	0(0.0)	
No	52(98.1)	122(100.0)		59(48.4%)	63(51.6%)	
Alcoholic intake			0.094			0.201
Never	35(66.0)	94(77.0)		48(81.3%)	46(73.0%)	
Stopped	0(0.0)	5(4.1)		0(0.0%)	5(7.9%)	
Occasionally	15(28.3)	17(13.9)		9(15.3%)	8(12.7%)	
Weekly	2(3.8)	2(1.6%)		1(1.7%)	1(1.6%)	
Daily	1(1.9)	4(3.3)		1(1.7%)	3(4.8%)	
Exercise			<0.001[¥]			0.835
Never	12(22.6)	86(70.5)		40(67.8%)	46(73.0%)	
Occasionally	20(37.7)	17(13.9		8(13.6%)	9(14.3%)	
Weekly	17(32.1)	10(8.2)		6(10.2%)	4(6.3%)	
Daily	4(7.5)	9(7.4)		5(8.5%)	4(6.3%)	
Age (years)	57.1 ± 5.9	59.6 ± 10.9	0.117	59.2 ± 11.2	60.0 ± 10.5	0.234
WBC	5.4(4.0–6.1)	5.2(4.2–6.5)	0.619	5.4(4.3–7.0)	5.1(4.1–6.3)	0.365
RBC	4.8(4.4–5.3)	4.5(4.0–4.9)	0.031[λ]	4.5(4.0–4.8)	4.6(4.0–5.0)	0.051
HB	12.7(11.5–13.6)	12.4(11.2–13.4)	0.408	12.5(11.4–13.5)	12.4(10.9–13.3)	0.348
PLT	220.5(172.5–266.0)	279.0(215.5–356.3)	<0.001[λ]	304(239.0–361.0)	256.0(207.0–337.0)	<0.001[β]
PCT	0.23(0.19–0.26)	0.17(0.13–0.22)	<0.001[λ]	0.17(0.14–0.21)	0.17(0.12–0.24)	<0.001[β]
MPV	10.1(9.5–10.8)	5.8(4.5–9.2)	<0.001[λ]	5.9(4.7–7.6)	5.4(4.3–10.4)	<0.001[β]
PDW	16.0(15.8–16.3)	17.6(15.4–19.3)	0.003[λ]	17.9(16.4–20.0)	16.6(12.9–18.5)	<0.001[β]

HPT: Hypertensives without stroke, HPT-S: Hypertensives with stroke, HGB: Haemoglobin Concentration, PLT: Platelet count, PCT: Plateletcrit, MPV: Mean Platelet Volume, PDW: Platelets Distribution Width, RBC-Red Blood Cell count, WBC: White Blood Cell count, JHS: Junior High School, SHS: Senior High School. [¥]Fischer Exact test of association, [ζ]Chi-Square test of association, [λ]Significant difference between controls and cases using Mann Whitney-U t-test, [β]Significant difference between controls, HPT and HPT-S using Kruskal Wallis test.

(below the cutoff) were given a bioscore of 0. Similar scores were also generated for MCP-1. The two markers were then combined to give a bioscore of three levels; 0, 1 and 2. ROC analysis was performed to test the performance of the bioscore model. Multiple logistic regression analysis was used to assess the chances of IL-197 10 and MCP-1 in predicting stroke among hypertensives after accounting for the effects of covariates (age, gender, occupational status and exercise activity). Missing data were excluded from the analysis and *p*-values of < 0.05 were considered statistically significant.

3. Results

3.1. Socio-demographic and clinical characteristics of study participants

A total of 175 participants consisting of 53 healthy controls (CS), 59 hypertensives without stroke (HPT) and 63 hypertensives with stroke (HPT-S) were included in the statistical analysis. There was no significant difference in age between controls, stroke-free, hypertensives, and hypertensives with stroke among the three study groups [57.1 ± 5.9 years vs 59.2 ± 11.2 years vs 60.0 ± 10.5 years, ($p > 0.05$). Gender was not associated with the study group ($p > 0.05$). Educational level, occupation and exercise activity were significantly different across the three groups ($p < 0.05$). However, smoking and alcohol intake were not associated with the study group. Except for white blood cell (WBC) count and haemoglobin concentration (HGB) that were not significantly different among study groups, the red blood cell count (RBC), platelet count (PLT), plateletcrit (PCT), mean platelet volume (MPV) and platelets distribution width (PDW) were significantly different among the three groups ($p < 0.05$). Table 1 displays the sociodemographic and clinical characteristics of the study groups.

3.2. Variability and predictability of individual cytokines among study groups

The HPT-S had significantly higher levels of MCP-1 compared to the HPT and CS groups ($p < 0.05$), with the CS and HPT having similar MCP-1 levels ($p > 0.05$). Similarly, The HPT-S had significantly higher levels of IL-10 compared to the HPT and the CS groups ($p < 0.05$), with the HPT and CS groups having similar IL-10 concentration ($p > 0.05$). There was no significant difference in IL-1β, IL-8 and IL-6 between the three study groups ($p > 0.05$) [Fig. 1].

In a receiver operator characteristics analysis for individual markers for predicting stroke among hypertensives, MCP-1 and IL-10 could significantly predict stroke among hypertensives [Fig. 2]. At a cut-off of 4.353 for MCP-1, the sensitivity and specificity for predicting stroke among hypertensives was 77.6% and 62.1% respectively. Also, at a cut-off of 12.781 for IL-10, the sensitivity and specificity for predicting stroke among hypertensives was 80.0% and 51.7% respectively [Table 2].

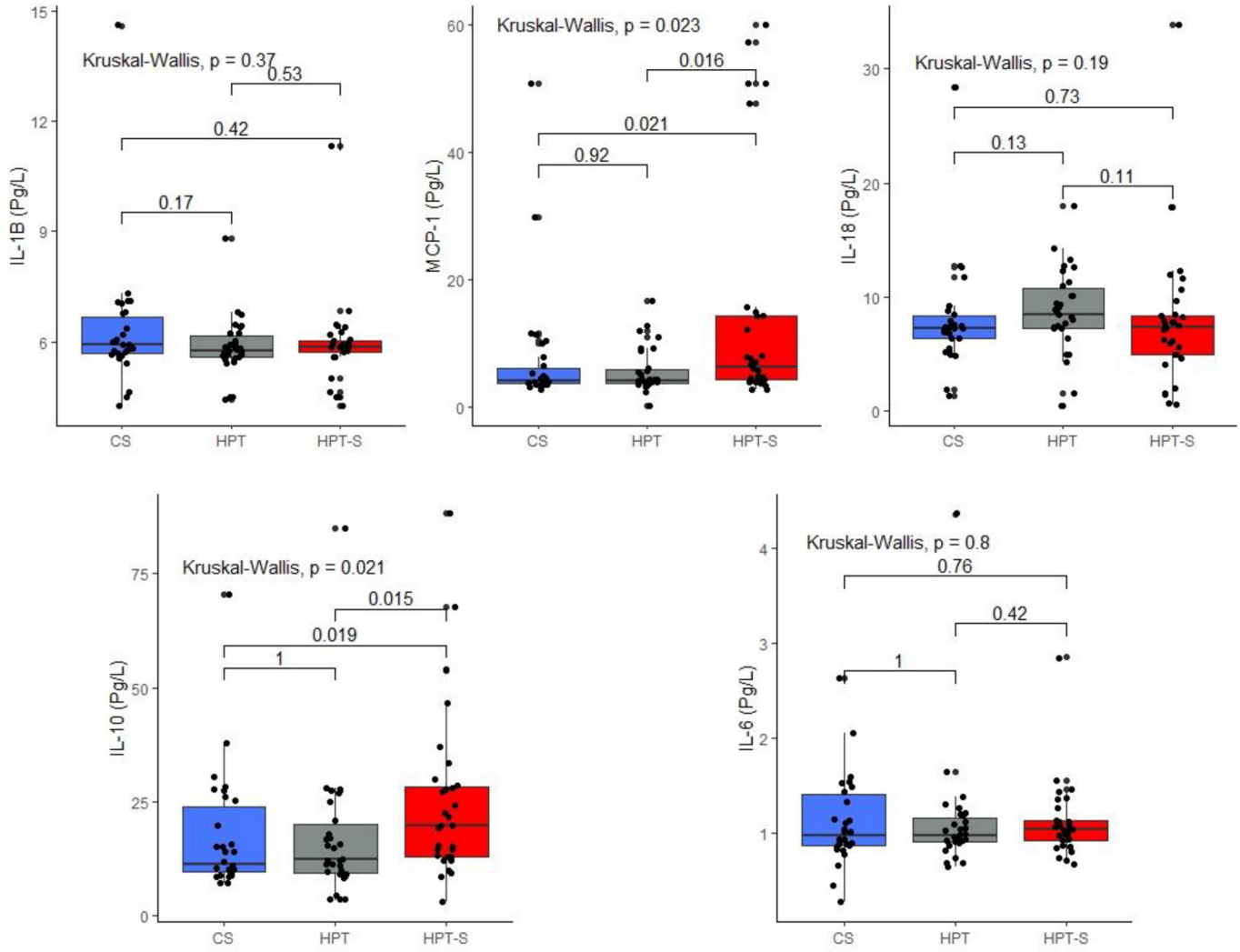

Fig. 1. Variability of cytokines among healthy controls (CS), hypertensives without stroke (HPT) and hypertensives with stroke (HPT-S).

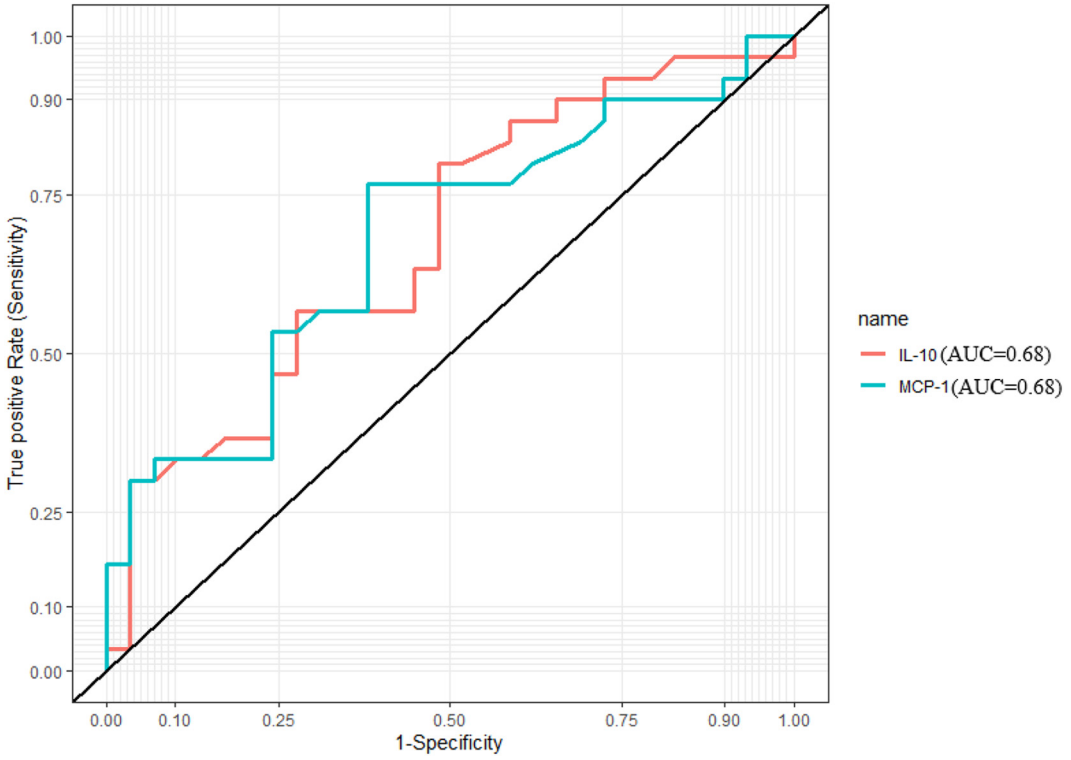

Fig. 2. Receiver operator characteristics of individual cytokines for predicting stroke among hypertensives.

3.3. Combined bioscore model of MCP-1 and IL-10 for predicting stroke among hypertensives

Combining IL-10 and MCP-1 in a bioscore model improved the predictive accuracy [Fig. 3]. In the model, having a bioscore of 1 or 2 could accurately predict stroke among hypertensives, with bioscore 2 having the highest and best accuracy of 0.81. At the same bioscore of 2, the sensitivity and specificity for predicting stroke among hypertensives was 77% and 84.0% respectively. At a bioscore of 1, the sensitivity and specificity for predicting stroke among hypertensives was 97.0% and 61.0% respectively [Table 3]. In a binary logistic regression, having a bioscore of 1 [aOR = 20.43, 95% CI (2.17–192.62), $p = 0.008$] or 2 [aOR = 26.00, 95% CI (2.92–231.31), $p = 0.003$] were significantly associated with over 20-folds increased odds of having stroke among hypertensives [Table 3].

4. Discussion

Hypertension has shown to be the strongest risk factor of atherosclerosis with inflammation culminating in stroke [35]. Growing evidence from epidemiological and clinical data suggests that inflammatory pathways are key mediators (pro-inflammatory and anti-inflammatory mediators) in the development of atherosclerosis, leading to stroke and other vascular events [35]. In view of this, markers that could predict or monitor the progression of hypertension to stroke are of research importance. In this study, we found significantly higher levels of IL-10 and MCP-1 among ischemic stroke survivors with hypertension compared to hypertensives without stroke and the healthy controls. Individual biomarkers of IL-10 and MCP-1 produced fair accuracies in predicting stroke among hypertensives whilst a combined bioscore of MCP-1 and IL-10 produced better accuracies, serving as powerful predictor of stroke among hypertensives.

An increase in production of pro-inflammatory cytokines and a decrease in the production of anti-inflammatory cytokines correlated with a larger infarct size in animal models and a worse clinical outcome [17]. Upregulation of anti-inflammatory cytokines associated in the process of stroke has been reported in animal studies [22,28], with few human studies explored.

In the present study, the finding of IL-10 being significantly higher among hypertensives with stroke compared to stroke free, hypertensives and the healthy controls is similar to the study of Pelidou *et al.* [36], who also found significantly higher levels of IL-10 secreting blood mononuclear cells among Swedish stroke patients compared to healthy controls. Vila *et al.* [17], reported lower levels of IL-10 to be associated with neurological worsening among acute ischemic stroke patients. Moreover, Van Exel *et al.* [25], in a follow-up study among the aged in the Netherlands found that lower IL-10 production were associated with increased mortality among stroke patients. The higher levels of IL-10 observed among hypertensives with stroke could reflect the anti-inflammatory cytokine upregulation in response to inflammation [22]. The time course of clinical strokes may play a role in the trajectory of IL-10. The present study recruited mostly chronic stroke survivors most of whom were on statin therapy which could upregulate production of IL-10 [27. 28]. However, after adjusting for statin use, the hypertensives with stroke had significantly higher levels of IL-10 compared to the stroke free hypertensives, suggesting that IL-10 upregulation may arise from other sources [Supplementary file, Table S1]. IL-10

Table 2
Individual diagnostic accuracies of IL-10 and MCP-1 for predicting stroke among hypertensives.

Marker	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	TP	TN	FP	FN	AUC
MCP-1	4.353 pg/mL	77.6 (58.7–88.3)	62.1 (43.9–77.3)	0.676	0.720	23	18	11	7	0.680
IL-10	12.781pg/mL	80.0 (62.2–90.7)	51.7 (34.5–68.6	0.6316	0.714	24	15	14	6	0.680

CI: confidence interval, IL: interleukin, MCP-1: monocyte chemoattractant protein-1, PPV: Positive predicting value, NPV: Negative predicting value, FP: False Positive; FN: False Negative, AUC: Area Under the Curve.

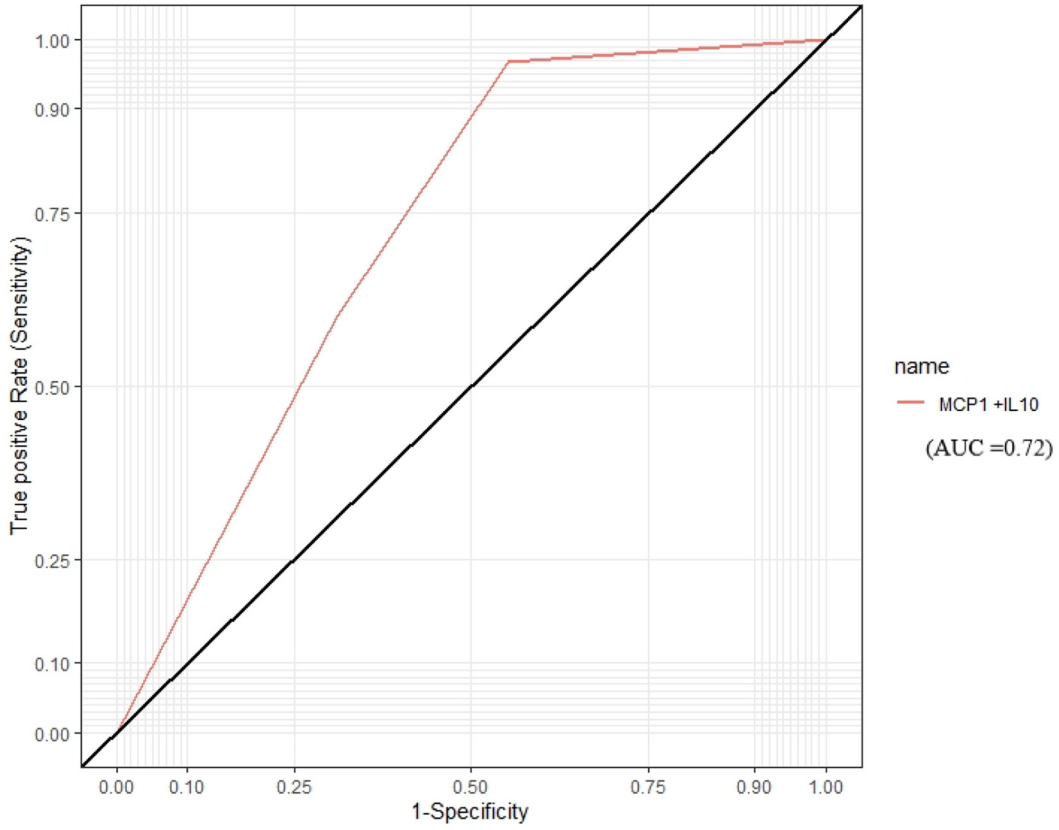

Fig. 3. Receiver operator characteristics of combined MCP-1 and IL-10 for predicting stroke among hypertensives.

upregulation has been reported in post ischemic stroke through the activation of ischemic and contralesional neurons resulting in the loss of inflammation during hypertension and stroke [26,27]. This has highlighted endogenous IL-10 as a potential therapeutic target to reduce inflammation and ischemic damage particularly under hypertension [28].

Elevation of MCP-1 in circulation of patients with atherosclerosis-associated complications implicate inflammatory processes, which contribute to the pathogenesis of ischemic stroke [18]. In support of this, we demonstrated that MCP-1 was significantly higher among hypertensive with stroke compared to the hypertensive without stroke and the healthy controls. In harmony with our study, Arakelyan et al. [37], reported significantly higher levels of MCP-1 among Czech Republic stroke patients compared to healthy controls. In another study, Zaremba et al. [38], found significantly higher levels of cerebrospinal fluid MCP-1 among stroke patients in comparison with the control group. However, in the same study, the serum level of MCP-1 did not differ between cases and controls.

Moreover, we found no significant difference in pro-inflammatory cytokines (IL-1β, IL-8 and IL-6) between the three study groups. The similarity in pro-inflammatory cytokines between the study groups could be due to the downregulation of IL-1β, IL-8 and IL-6 as a result of the increased IL-10. This is because IL-10 upregulation occur in later stages of stroke via the activation of ischemic and contralesional neurons resulting in the downregulation of inflammation [26,27].

The significantly higher levels of IL-10 and MCP-1 among hypertensives with stroke suggest that these cytokines could be useful in predicting the progression of hypertension to stroke. To test this, we assessed the capabilities of the individual and combined bioscore of MCP-1 and IL-10 to discriminate between hypertension with stroke and hyertension without stroke using ROC curve analysis. Among these, the individual biomarkers produced fair accuracies whilst the combined bioscore produced higher accuracies, with a bioscore of 2 being the best predictor of stroke among hypertensives. Having a biscore of 2 could predict stroke with a sensitivity of 77.0% and specificity of 84%. The same bioscore was associated with over 20-folds increased odds of having stoke among hyperytensives. This study finding reveals that combined effect of IL-10 and MCP-1 could be a powerful predictor of stroke among hypertensives and the combined markers can be used to monitor hypertensives who are at risk of developing stroke.

Post-stroke infections and other complications affects the level of pro- and anti-inflammatory cytokines, however, the current study did not factor these complications in our data collection since all sampling were done immediately stroke patients were admitted.

One limitation of this study is the inability of researchers to recruit stroke patients of the same stage. Some stroke patients were in the early stages whilst others were in the later stages. However, this was controlled in the statistical analysis. Furthermore, it was a single center study hence findings cannot be generalized. Again, the sample size was modest and

Table 3
The predictive accuracies of combined bioscore of MCP-1 and IL-10.

MCP1 + IL-10	Sensitivity (95% CI)	Specificity (95% CI)	LR+	LR-	Accuracy	aOR
0	1.00 (0.86–1.00)	0.00 (0.00–0.14)	1.00	–	0.51	1 (ref)
1	0.97 (0.81–1.00)	0.61 (0.36–0.75)	1.75	0.07	0.79	20.43 (2.17–192.64)*
2	0.77 (0.42–0.86)	0.84 (0.51–0.91)	1.93	0.58	0.81	26.00 (2.92–231.31)*

Logistic regression model (aOR) was adjusted for age, gender, occupational status and exercise activity; CI: Confidence Interval; IL-10: interleukin-10; MCP-1: monocyte chemoattractant protein-1; LR+: Likelihood Ratio Positive; LR: Likelihood Ratio Negative.

could be increased in future studies while exploring other biomarkers for their predictive associations between hypertensives without stroke and normotensives.

5. Conclusion

Higher levels of IL-10 with a concomitant level of MCP-1 could serve as a good predictor of stroke among hypertensives. Subsequently, MCP-1 may prove useful as a therapeutic target for atherosclerosis in hypertensives. Combined bioscore of MCP-1 and IL-10 could serve as a good predictor of stroke among hypertensives.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary file 1 denote regression analysis of the effect of covariate on cytokine levels.

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