

Serum Lipoprotein-a [Lp(a)] is more associated with Acute Ischemic Stroke than LDL- cholesterol among Nigerian Africans

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Abstract

INTRODUCTION: Stroke affects Africans at an earlier age than Caucasians but the contribution of emerging risk markers like lipoprotein-a [Lp(a)] to acute ischemic stroke (AIS) among Indigenous Africans is unknown. We hypothesized that serum lipoprotein-a [Lp(a)] may be associated with acute ischemic stroke (AIS), and perform better than low-density lipoprotein cholesterol (LDL-c) in predicting AIS in Nigerian Africans.

METHOD: A comparative cross-sectional study was conducted with 92 patients with clinico-radiologic diagnosis of AIS and 92 age- and sex-matched controls (Ethical approval: UI/EC/24/0442). Stroke subtype was documented using the TOAST criteria while severity was assessed using the NIHSS score. Serum Lp(a) was analysed using ELISA (Elab science E-EL- H0160). The Shapiro-Wilks test was used to test the normality of data while conditional (step-wise) multi-variable logistic regression was used to investigate the independent association between serum Lp(a) and AIS. Model I adjusted for age and sex, II for years of education, III for alcohol use and smoking, and IV for LDL-c, hypertension and Diabetes. The respective aOR(95%CI) were reported with p-values set at <0.05.

RESULTS: The mean (SD) age (years) was 63.9 (13.97) for cases, 61.9 (15.06) for controls and 53% were males. The median (IQR) Lp(a) (mg/dl) was 88.88 (242.85) among cases and 22.45 (103.50) for controls, ($p < 0.001$). Among the stroke population, the mean NIHSS score was 12.39 (5.79). Using the TOAST criteria, 41 (44.6%) had small vessel disease, 21 (22.8%) undetermined etiology, 16 (17.4%) cardioembolic and 13 (14.1%) had large vessel disease. Elevated serum Lp(a) 1.006 (1.001 – 1.011), but not elevated serum LDL-c 1.013 (0.998 – 1.028), was independently associated with AIS.

CONCLUSION: Nigerian Africans with AIS have elevated serum Lp(a) and it may be independently associated with AIS in the population. Our findings require further validation in larger cohorts.

INTRODUCTION

Globally, stroke is a recognized cause of death, disability, and dwindling economic potentials. Africans develop stroke at an earlier age than Caucasians but the contribution of emerging risk markers like lipoprotein-a [Lp(a)] to acute ischemic stroke (AIS) among Indigenous Africans is unknown.¹ Traditional lipid markers, including low-density lipoprotein cholesterol (LDL-c), have been the mainstay of atherosclerotic cardiovascular disease (ASCVD) risk assessment for decades, but the paradigm is shifting.^{2,3} Emerging risk factors may be more relevant in the aetiology of early-onset stroke and among younger patients.⁴ Given that stroke among Africans develop at an earlier age^{5,6}, it may be helpful to characterize emerging risk factors and examine its contribution to varying stroke subtypes.^{4,7} Among Caucasian population, independent associations of Lp(a) and risk of coronary heart disease and stroke have been documented^{2,8}, with sparse data from African Ancestry populations.^{3,9} This is further imperative as serum Lp(a) has wide genetic, geographic and ethnic variability.¹⁰ Curiosity hence exists if

serum Lp(a) may have a stronger association with ischemic stroke among Nigerian Africans, and if it performs better than traditional LDL-c in predicting AIS in Nigerian Africans.

METHODS

This comparative cross-sectional study investigated the contribution of serum lipoprotein-a [Lp(a)], an infrequently measured cardiovascular risk marker in routine clinical care^{8,10}, to acute ischemic stroke (AIS) among Nigerian Africans. The study was conducted at the University College Hospital (UCH), a tertiary stroke care center in Ibadan, Southwest Nigeria. Participants included 92 adults with clinically and radiologically confirmed acute ischemic stroke, as well as 92 age- and sex-matched stroke-free controls. (Ethical approval: UI/EC/24/0442).¹¹ Data obtained included detailed clinical and stroke assessments, neuro-imaging, as well as laboratory assays. Stroke subtype was documented using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria while severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) score. Serum Lp(a) concentrations were analysed using Enzyme Linked Immunosorbent assay (ELISA), measured primarily from prospectively recruited patients.

At presentation, 5ml of venous blood was drawn from individual participants and dispensed into a Gel/Clot activator bottle. The specimen bottle was centrifuged (after 30 minutes of specimen collection, to allow for full clot retraction) at 3000xg for 15 minutes and the serum obtained stored at a temperature of -20C at the UCH Chemical Pathology Laboratory until batched analysis within 3 months of specimen collection. Serum Lp(a) concentration was measured using Enzyme Linked Immunosorbent assay according to the manufacturer's specification (Elab science E-EL- H0160, on StatFax 4200 ELISA Reader [USA]) by chemical pathologists (CU, BC, EN). Enzymatic method was used to analyze serum total cholesterol [TC] (cholesterol-oxidase), triglyceride [TG] (lipase/glycerol phosphate-oxidase) and high-density lipoprotein cholesterol [HDL-C] (direct HDL PEGME) on LandWind C 100 plus chemistry auto-analyser, while Friedwald equation was used to calculate LDL-c.

The Shapiro-Wilks test was used to test the normality of data. To determine the relationship between AIS and risk factors including serum Lp(a), bivariate analyses were performed using relevant statistical tests: chi-square (or Fisher's exact) test for categorical variables; independent students t-test for normally distributed continuous variables, or its non-parametric equivalent (Mann-Whitney U) for non-normally distributed continuous data. Conditional (stepwise) multi- variable logistic regression was used to investigate the independent association between serum Lp(a) and AIS. Model I was adjusted for age and sex, model II was adjusted for years of education in addition to covariates in model I, model III was adjusted for alcohol and smoking use in addition to covariates in model II, and model IV was adjusted for LDL-c, hypertension, Diabetes Mellitus (DM) in addition to covariates in model III. The respective aOR(95%CI) were reported with significant p-values set at <0.05. Further, the comparative abilities of serum Lp(a) and LDL-c to discriminate AIS were investigated using a receiver operating characteristics (ROC) curve with respective areas under the curve (AUC) and 95% confidence intervals (CI)

RESULTS

The mean (SD) age (years) was 63.9 (13.97) for cases, 61.9 (15.06) for controls ($p = 0.275$) and 53% were males. The median (IQR) Lp(a) (mg/dl) was 88.88 (242.85) among cases and 22.45 (103.50) for controls, ($p < 0.001$) while the median (IQR) LDL-c (mg/dl) was cases 111.50 (61.50) v controls 99.50 (42.75) ($p = 0.133$). Among the stroke population, the mean NIHSS score was 12.39 (5.79). Using the TOAST criteria, 41 stroke participants (44.6%) had small vessel disease, 21 (22.8%) undetermined etiology, 16 (17.4%) cardioembolic and 13 (14.1%) had large vessel disease. There was no statistically significant difference between serum Lp(a) concentration and ischemic stroke severity or subtype. Effect sizes of stroke risk factors as well as serum Lp(a) in the univariate analyses and across models I – III are as shown in Table 1. In the final model (IV) (Figure 1), the risk factors independently associated with AIS in descending order of aOR (95% CI) were hypertension 8.333 (1.873 – 37.040), higher years of education 1.274 (1.083 – 1.500), older age 1.076 (1.023 – 1.133), and elevated serum Lp(a) 1.006 (1.001 – 1.011), but not elevated serum LDL-c 1.013 (0.998 – 1.028) (Table 1). In the ROC curve designed to identify participants with AIS, serum Lp(a) had a higher AUC (95% CI) [0.59 (0.49 – 0.69)] than LDL-c [0.55 (0.45 – 0.65)].

CONCLUSION AND FUTURE DIRECTIONS

Nigerian Africans with AIS have elevated serum Lp(a) and it may be independently associated with AIS in the population. Given its high atherogenicity and morphologic similarity to plasminogen, Lp(a) may be prothrombotic and inflammatory in atherosclerotic strokes.³ This study provides preliminary evidence supporting the potential contribution of an infrequently measured risk marker to acute ischemic stroke pathobiology among Nigerian Africans. The observed modest association may be due to a higher prevalence of small vessel disease attributable to hypertension in the population as against the more atherosclerosis-mediated large-vessel disease.^{1,12} Of note, serum Lp(a) has been shown to independently and additively, alongside LDL-c, contribute to atherosclerotic cardiovascular disease (ASCVD) risk¹³, even as LDL-C lowering therapies may not effectively offset Lp(a)-mediated risk.²

Our findings potentially highlight an unmet therapeutic gap for secondary stroke care with implications for recurrent stroke in a high-risk population, as has been highlighted in regional studies.^{14–17} Given the reported wide biological, ancestral and genetic variability of Lp(a) and higher values among African ancestry individuals^{2,3,18}, it will be helpful to document serum Lp(a) thresholds¹⁷ relative to specific ischemic stroke pathologic subtypes, other stroke types and outcome.¹⁷ Our findings need to be further validated in larger multi-center cohorts and may have public health implications in a region, where investigating the benefits of emerging Lp(a)-lowering therapies ensures equitable access to evidence-based, life-saving interventions.

Declarations

Written informed consent was obtained from all participants or, where stroke prevented direct consent, from their legally authorized representatives or next-of-kin.

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Data Availability statement: The datasets generated during and/or analysed during the current study are not publicly available due restrictions from the local institutional review board (IRB) but are available from the corresponding author on reasonable request and approval from the local IRB.

CONFLICTS OF INTEREST: None

CLINICAL TRIAL NUMBER: Not applicable.

HUMAN ETHICS AND CONSENT TO PARTICIPATE DECLARATIONS: Written informed consent was obtained from all participants or, where stroke prevented direct consent, from their legally authorized representatives or next-of-kin.

CONSENT TO PUBLISH DECLARATION: Not applicable.

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Tables

Table1: Conditional logistic regression model demonstrating the relationship between serum Lp(a) and acute ischemic stroke (AIS)

Lp(a), lipoprotein-a, LDL-c, low-density lipoprotein cholesterol

Co-variates	Crude	Model I	Model II	Model III	Model IV
Serum Lp(a)	1.006 (1.003, 1.009)	1.008 (1.004, 1.012)	1.006 (1.002, 1.011)	1.006 (1.002, 1.010)	1.006 (1.001, 1.011)
Age	1.015 (0.994, 1.037)	1.061 (1.021, 1.103)	1.071 (1.026, 1.117)	1.068 (1.021, 1.116)	1.076 (1.023, 1.113)
Female Sex (male ref)	0.957 (0.537, 1.708)	0.234 (0.088, 0.622)	0.569 (0.180, 1.795)	1.049 (0.297, 3.704)	1.108 (0.256, 4.796)
Years of education	1.194 (1.104 - 1.291)	-	1.240 (1.101- 1.397)	1.275 (1.117 - 1.454)	1.274 (1.083 - 1.498)
Alcohol use (ref never)	0.388(0.164, 0.921)	-	-	1.923(0.307, 12.043)	4.288(0.546, 32.766)
Smoking use (ref never)	CNC**	-	-	CNC**	CNC**
HTN, yes	9.963(4.612, 21.520)	-	-	-	8.333(1.873, 37.040)
DM, yes	1.919 (0.809, 4.552)	-	-	-	3.663 (0.588, 23.256)
Serum LDL-c	1.009 (1.000, 1.017)	-	-	-	1.013 (0.998, 1.028)
Nagelkerke R square	-	0.338	0.472	0.556	0.675

CNC**Could not converge

Model I adjusted for age and sex,

model II included variables in model I plus years of education,

model III included variables in model II plus alcohol use and smoking, and

model IV included variables in model III plus LDL-c, hypertension and Diabetes.

Figures

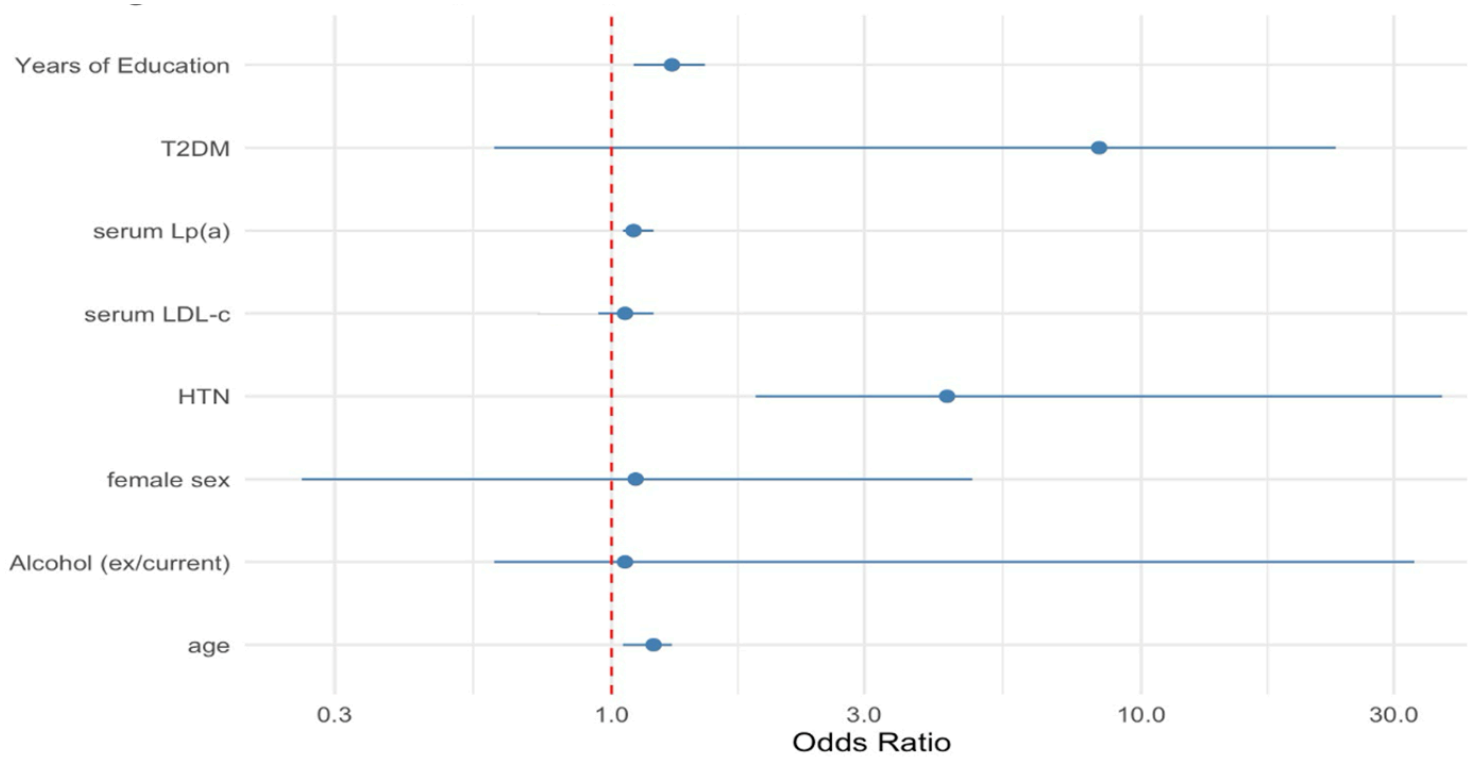


Figure 1

Factors independently associated with acute ischemic stroke (AIS) among Nigerian Africans

HTN: hypertension, T2DM: Type 2 Diabetes mellitus

LDL-c low-density lipoprotein cholesterol