Left Ventricular Hypertrophy in Young Africans With First Ever Stroke in Tanzania: A Prospective Cohort Study

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Abstract

Background: Left ventricular hypertrophy is a pathophysiological response to chronic hypertension and is an independent risk factor for vascular events. We sought to determine the magnitude, correlates and prognosis of left ventricular hypertrophy in young patients presenting with their first stroke at a tertiary hospital. We also sought to determine the accuracy of electrocardiography using Sokolow-Lyon and Cornell criteria in detecting left ventricular hypertrophy compared to echocardiography.

Methods: This cohort study prospectively recruited consecutive stroke patients aged 18-45 years who had undergone brain imaging, electrocardiogram and transthoracic echocardiography. Baseline data were recorded and correlates of left ventricular hypertrophy were identified using the modified Poisson regression. Follow-up for functional outcomes was performed to 30-days using the modified Rankin Scale.

Results: We enrolled 101 participants with first ever stroke. The mean age of patients was 39.7 years and the mean National Institutes of Health Stroke Score was 18, reflecting severe disability. Brain imaging revealed ischemic strokes in 60 (59.4%) of patients and of those with intracerebral hemorrhage, 33 (86.8%) were localized to the basal ganglia, in keeping with a hypertensive etiology. Left ventricular hypertrophy was present in 76 (75.3%; 95% CI 65.7% − 83.3%), and 30 (39.5%) and 28 (36.8%) had moderate to severe degree respectively. Young adults with left ventricular hypertrophy were more likely to have a higher systolic and diastolic blood pressure on arrival 156.3±19 and 96.4±10.6 respectively. On multivariable analysis, lack of antihypertensive medication was associated with left ventricular hypertrophy {adjusted risk ratio 1.42 (95% CI: 1.04−1.94). The sensitivity and specificity for Sokolow-Lyon in detecting left ventricular hypertrophy was 27% and 78%, and for Cornell was 32% and 52% respectively. At 30-days, functional independence was achieved in 12 (12.4%) and almost half had died.

Conclusions: There is a high burden of left ventricular hypertrophy in young patients with first stroke. Untreated hypertension is the likely etiology associated with a high 30-day mortality. Our findings did not support the use of the electrical voltage criteria for detecting left ventricular hypertrophy. We recommend low cost interventions such as blood pressure screening and control to reduce this burden in the young.

Background

Stroke is the leading cause of death and disability in low and middle income countries (LMICs) accounting for 80% of the global burden (1). Cardiovascular diseases, particularly hypertension, is the leading risk factor for stroke in both high and LMICs and is responsible for 20-50% of all strokes (2−4). In sub Saharan Africa (SSA) including Tanzania, 50% of stroke among the young population is attributed to uncontrolled hypertension (5) and 45% of all stroke cases could be prevented by adequate blood pressure control (6,7).

Left ventricular hypertrophy (LVH) is a common complication of long standing uncontrolled arterial hypertension, occurring as a pathophysiological adaption to chronic increased afterload (8). This

abnormal increase in the left ventricular mass serves as an independent predictor for coronary events, heart failure, ventricular arrhythmias, stroke and peripheral arterial disease (9). Previous reports have indicated an increased incidence of stroke among elderly with LVH and is included in the original 10-year Framingham stroke risk score for prediction of stroke in the geriatric population (10). In SSA, there is a high burden of LVH (up to 50%) particularly among untreated hypertensive patients (11). A study in West Africa revealed that more than half of the stroke patients were found to have LVH by electrocardiogram. Independent predictors for LVH were: younger age (<45 years), female gender and uncontrolled hypertension (12).

Transthoracic echocardiography (TTE) is a noninvasive modality of choice to assess cardiac structure and function (including the detection of LVH) (13). It is considered gold standard and superior to the 12-lead electrocardiogram (ECG) for diagnosing LVH (14). In Tanzania, little is known about the burden and outcomes of LVH among young adults with stroke. We aimed to investigate the magnitude, correlates and outcomes of LVH among young adults with stroke admitted at a tertiary hospital in Tanzania. We also sought to determine the accuracy of electrocardiography using Sokolow-Lyon and Cornell criteria in detecting LVH compared to echocardiography.

Methods

Study design and population:

This prospective cohort study was conducted at Muhimbili University of Health and Allied Sciences Academic Medical Center (MAMC), medical wards in Dar es Salaam, Tanzania. MAMC is a tertiary teaching hospital that offers super specialized medical care to all specialties and receives referral patients from both public and private hospitals from all over the country.

We recruited consecutive participants who were admitted at MAMC with a clinical diagnosis of first ever stroke as classified by the World Health Organization (WHO) (15) between June 2018 to January 2019. Participants were eligible for enrollment if they were aged between 18 to 45 years. Written informed consent was obtained from either the participants or their next of kin if the participant was unable to consent prior to study enrollment.

Data collection:

An interviewer based structured questionnaire was administered to all study participants or their caregivers capturing the following: sociodemographic information, mobile numbers, premorbid stroke risk factors (e.g. hypertension, diabetes mellitus (DM), smoking, alcohol consumption and HIV infection). Medication history for hypertension, diabetes and HIV was also obtained.

Physical examination included measurement of blood pressure (BP) using a standard digital BP machine, AD Medical Inc. Three BP readings were collected spaced 5 minutes apart, while the participant was at rest and an average BP was computed. Hypertension was defined as a systolic blood pressure (SBP)

≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg or those on current anti-hypertensive therapy according to the Joint National Committee 7 (JNC-7) definition (16). All participants had their waist and hip circumference measured using a tape measure and recorded in centimeters. The waist-hip ratio was interpreted according to the WHO guidelines; in males the ratio of ≥0.90 and females ≥0.85 was regarded as substantially increased (17).

Capillary fingertip blood samples were collected to check for random blood glucose (RBG) levels and HIV rapid testing using a glucometer GLUCOPLUS^{TM} and SD Bioline respectively. A fasting blood glucose (FBG) sample was collected the following morning for participants with (RBG) levels of ≥11.1 mmol/l. DM diagnosis was defined as a RBG reading of ≥ 11.1 mmol/l or a FBG reading of ≥ 7 mmol/l. For participants who were HIV reactive to SD Bioline, were tested also using Unigold Biotech.

We aseptically collected 5mls of venous blood from each study participant and analyzed for random total cholesterol and low-density lipoprotein using BIO- SYSTEMS machine.

A non-contrast brain computed tomography scan (NCCT) using GE Healthcare Optima or magnetic resonance imaging (MRI) with GE SIGNA CREATOR were performed on study participants on admission and images interpreted by a senior radiologist.

TTE using GE Medical Systems was performed and interpreted by a qualified cardiologist. Evidence of LVH was defined according to the European Society of Cardiology/American Society of Echocardiography as a measure of severity of septal thickness in 4 chamber view at mid-septum in the end of diastole (18). A mid septal diameter of 11 – 13mm in males and 10 – 12 mm in females was defined as mild LVH, 14 – 16 mm in males and 13 – 15 mm in females as moderate LVH and ≥17 mm in males and ≥16 mm in females as severe LVH (19).

An ECG using Bionet model Cardio7 machine was performed on the study participants to look for evidence of LVH using the Sokolow-Lyon and Cornell criteria defined as S in V1 plus R in V5 or V6 required to surpass 3.5 mV (20), and the S in V3 plus R in aVL required to surpass 2.0 mV in females and 2.8 mV in males (21) respectively. Atrial fibrillation was defined as the presence of irregular RR intervals and no discernible distinct P waves (22).

Stroke severity was assessed using the National institute of health stroke scale (NIHSS) (15) and outcomes were assessed using the modified Rankin Scale (mRS) (15) at 24 hours, 72 hours, 7 days, 14 days and at 30 days from admission. Functional independence was defined as mRS score of 0-2.

Data analysis:

Data was analyzed using SPSS version 20.0. Continuous variables were summarized and presented as means and standard deviation (SD). Categorical variables were summarized as frequencies and proportions. Comparison between proportions were done using Pearson's Chi square test or Fisher's exact test. The outcome variable (LVH) was common, hence we used the modified Poisson regression to

determine factors that were independently associated with LVH. All covariates with a p-value of <0.2 in bivariable analysis were included in the multivariable analysis model. Unadjusted and adjusted risk ratios (RR), 95% confidence intervals (CI) and corresponding p values were obtained from the models. A two-tailed significance level was set as a p value of < 0.05. Receiver operator characteristics (ROC) analysis was performed to estimate the performance of the electrical voltage criterions (Sokolow-Lyon and Cornell criterion) to the gold standard TTE in detecting LVH.

Results

There were a total of 484 medical admissions of patients aged ≤45 years between June 2018 to January 2019, of whom 128 (26.4%) participants met the World Health Organization (WHO) clinical diagnosis of first ever stroke (15). We excluded 27 (21.1%) participants for the following reasons: unable to consent 5 (3.9%), did not complete brain imaging 6 (4.7%) and did not undergo TTE 16 (12.5%). The remaining 101 young adults with stroke were recruited. There were 4 participants who were lost to follow-up and were excluded from the outcome analysis, Figure 1.

The proportion of LVH confirmed by TTE among the young stroke participants was 76 (75.3%; 95% CI 65.7% − 83.3%). The mean age±SD of the recruited participants was 39.7±2 years, whereas the mean NIHSS was 18.3±9.2, reflecting severe disability. Less than a third of the study participants had health insurance 29 (28.7%). The majority of the young stroke participants had a previous history of hypertension 66 (65.3%). The overall mean systolic and diastolic blood pressures at enrollment were 153.5±20.1 mmHg and 94.5±11.4 mmHg (Table 1). However, the young stroke participants with LVH were more likely than without LVH to have a higher systolic and diastolic blood pressure, 156.3 ± 19 vs 145.1 ± 19.5 mmHg, p=0.017 for systolic blood pressure (SBP) and 96.4 ± 10.6 vs 89 ± 12.2 mmHg, p=0.01 for diastolic blood pressure (DBP) respectively. The majority of young stroke participants had moderate 30 (39.5%) to severe 28 (36.8%) LVH as summarized in figure 2.

Table 2 summarizes the stroke subtype among the young stroke participants with LVH and without LVH. Ischemic stroke was the major stroke subtype accounting for 60 (59.4%) of all young strokes. There was no statistical significant difference in stroke subtype among the two groups. The location of the hemorrhages was intracerebral in 38 (92.7%) and subarachnoid in 3 (7.3%). Among those with intracerebral hemorrhage, 33 (86.8%) were in the basal ganglia.

Factors associated with LVH are summarized in Table 3. In bivariable analysis, factors that were significantly associated with LVH among the young stroke participants were: hypertension, not on anti-hypertensive medication, family history of hypertension and hypercholesteremia. In multivariable analysis after adjusting for other factors, lack of anti-hypertensive medication was the only independent factor for LVH {adjusted RR 1.42 (95% CI: 1.04−1.94)}.

Mortality at 30 days was 42 (43.3%), with no statistically significant difference in mortality between young strokes with and without LVH. A total of 55 (56.7%) participants survived to 30-days, those who

achieved functional independency (mRS 0-2) were 8 (11%) and 4 (16.7%) among young strokes with LVH and without LVH respectively (Table 4).

The sensitivity and specificity analysis for the detection of LVH using the electrical voltage criteria (Sokolow-Lyon and Cornell criteria) are presented in Table 5. ECG could not be performed on 10 young stroke participants and were excluded from this analysis. The sensitivity and specificity for the Sokolow-Lyon criteria in detecting LVH was 27% and 78% and for Cornell criteria was 32% and 52% respectively. The ROC analysis was also carried out and the results are shown in Figure 3. Both criterions did not reach statistical significance, for Sokolow-Lyon criteria area under the curve (AUC)= (0.55 [95% CI 0.42 − 0.69], p=0.44) and Cornell criteria AUC= (0.48 [95% CI 0.33 − 0.63], p=0.78).

Discussion

This study aimed to investigate the burden and early outcomes of LVH among young adults with first ever stroke admitted at a tertiary hospital in Tanzania. We found that three-quarters of young stroke participants had LVH as diagnosed by TTE, which is higher than that described in a West African study by Adeoye et al, were 55% of the blacks (mean age of 59.1±13.2 years) with first stroke had LVH (12). The authors also found that younger age ≤45 years was independently associated with LVH, suggesting an underlying genetic factor in the pathogenesis which merits further investigation. Our findings also reveal a higher proportion of LVH compared to studies in high income countries in comparable populations. For instance, in the United States, Luciana et al found 30% of young adults with first stroke had LVH on TTE (23) and Levy et al describes a prevalence of 6% among adults under 30 years (24). This difference in proportions could be explained by the different ethnicity; ours exclusively an African population. Numerous reports have indicated that ethnicity plays an important role in the epidemiology of LVH (13,25,26); Compared to whites, Africans with or without stroke are more likely to have LVH across all age groups.

LVH is the increase in ventricular mass either due to an increase in wall thickness, in cavity size, or both (9). Hypertension plays a crucial role in the pathogenesis of LVH, which in turn is an independent risk factor for end organ damage (27). In this study, young stroke participants with LVH were statistically more likely to have uncontrolled hypertension supported by the fact that they had a higher mean systolic and diastolic blood pressures on hospital arrival compared to those without LVH. Similarly, more than a third of the young stroke participants with LVH had deep basal ganglia intracerebral hemorrhage on brain imaging, in keeping with the known pathophysiology of this stroke subtype. Hypertensive hemorrhages typically occur in these regions as the penetrating arteries are susceptible to rupture due to hypertension (28).

Remarkably, the majority of our young stroke participants had moderate to severe degree of LVH by TTE. This implies that the elevated blood pressure readings observed in our study population were less likely a result of the auto-regulatory mechanisms commonly seen in acute stroke, but rather a chronic adaptation to long standing undiagnosed hypertension. Longitudinal studies have established that cardiac end

organ damage progresses from young adulthood to middle age and is compounded by hypertension, DM and tobacco smoking (29). Similarly, several studies have demonstrated an increased risk of stroke among individuals with LVH secondary to hypertension (30,31). This merits the need for early screening to detect hypertension during the adolescent period at secondary schools, long before end organ damage manifests. Further research is needed on the etiology of hypertension in young African adults.

It is notable that not taking anti-hypertensive medications was the only independent factor associated with LVH among the young stroke participants, in line with other studies (32). In this study, the majority of young participants had premorbid hypertension. Non-adherence or undertreated hypertension are likely causes of this uncontrolled hypertension and warrants further research. Possible causes of non-adherence to treatment could be lack of insurance, which was seen in less than a third of the study participants. The need for treatment and control of hypertension cannot be overemphasized in SSA (4,33). This calls for urgent community awareness and campaigns promoting the importance of drug adherence in chronic illnesses.

In this study, we observed a high 30-day mortality, seen predominantly in patients with LVH. This suggests that primary prevention is the main route to reducing the burden from LVH and stroke, as once young adults succumb to stroke, their prognosis is generally poor and leads to a decline in the family and nation's economy.

Given the cost and availability of TTE, we also aimed to assess the performance of the electrical voltage criteria for detecting LVH compared to TTE. We found that both the Sokolow-Lyon and Cornell criteria had a low sensitivity, moderate specificity and poor performance in detecting LVH in our population, making it a less accurate and unreliable method. Therefore, the key public health message from this research is that efforts should be centered at promoting low cost interventions such as blood pressure screening, treatment and control which could reduce the burden of LVH and stroke in young Africans.

Our study had the following limitations; it was a single center with a small sample size therefore there was limited power to detect the differences between the two groups and the results cannot be generalized.

Conclusions

We identified a high proportion of young strokes with LVH. Untreated hypertension was the likely etiology and was associated with a high 30-day mortality. Further studies are recommended to investigate the etiologies of hypertension and causes of non-adherence or under treatment with medications. This will help identify sustainable interventions that will support prevention, detection and treatment of hypertension in young adults to reduce the burden of stroke.

List Of Abbreviations

AF: Atrial Fibrillation

DALYS: Disability Adjusted Life Years

DWI: Diffusion Weighted Image

FBG: Fasting Blood Glucose

HIV: Human Deficiency Virus

mRS: Modified Rankin Scale

NIHSS: National Institute of Health Stroke Scale

SSA: sub Saharan Africa

TTE: Trans thoracic echocardiography

WHO: World Health Organization

Declarations

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Tables

Table 1: Baseline characteristics of the young stroke participants, N=101

Variable	N	%
Female	59	58.4
Mean age±SD	39.7±2	
Residency		
Dar es Salaam	77	76.2
Marital status		
Ever married	74	73.3
Never married	27	26.7
Insured	29	28.7
Medical history		
Previous hypertension	66	65.3
Previous diabetes	13	12.9
HIV infection	9	8.9
Ever smoked	6	5.9
Ever consumed alcohol	23	22.8
Clinical characteristics		
NIHSS Mean±SD	18.3±9.2	
Systolic blood pressure Mean±SD	153.5±20.1	
Diastolic blood pressure Mean±SD	94.5±11.4	

NIHSS- National institute of health stroke scale, SD- Standard deviation

Table 2: Stroke subtype among young stroke participants with and without LVH, N=101

Stroke subtype	LVH n=76 (%)	without LVH n=25 (%)	Total n=101 (%)	p value
Ischemic	42 (55.3)	18 (72.0)	60 (59.4)	0.139
Hemorrhagic	34 (44.7)	7 (28.0)	41 (40.6)	0.164

Table 3: Factors associated with LVH among young stroke participants

Factor	Total	No. with LVH (%)	Unadjusted RR (95% CI)	p value	Adjusted RR (95% CI)	p value
Age group (years)						
18 - 30	11	45.5	1		1	
31 - 45	90	78.9	1.73 (0.91 - 3.34)	0.10	0.93 (0.52 - 1.64)	0.80
Gender						
Female	59	72.2	1			
Male	42	81.0	1.12 (0.91 - 1.42)	0.25		
Hypertension						
No	35	62.9	1		1	
Yes	66	81.8	1.30 (1.01 - 1.83)	0.04	0.79 (0.48 - 1.32)	0.37
Not on anti hypertensives						
No	27	63.0	1		1	
Yes	39	94.9	1.51 (1.02 - 2.32)	0.01	1.42 (1.04 - 1.94)	0.03
Family history of hypertension						
No	59	64.4	1		1	
Yes	42	90.5	1.41 (1.14 - 1.74)	0.002	1.13 (0.92 - 1.39)	0.26
Diabetes						
No	88	75.0	1			
Yes	13	76.9	1.03 (0.74 - 1.41)	0.88		
Smoking						
No	95	74.7	1			
Yes	6	83.3	1.12 (0.77 - 1.63)	0.57		
Atrial fibrillation						
No	88	75.0	1			

Yes	3	66.7	0.89 (0.39 - 1.99)	0.78		
Increased waist-hip ratio						
No	13	46.2	1		1	
Yes	88	79.5	1.72 (0.95 - 3.13)	0.07	1.22 (0.74 - 2.02)	0.43
Increased LDL						
No	65	73.8	1		1	
Yes	25	84.0	1.14 (0.95 - 1.46)	0.13	1.03 (0.83 - 1.27)	0.81
Hypercholesteremia						
No	66	72.7	1		1	
Yes	28	89.3	1.23 (1.05 - 1.55)	0.01	1.08 (0.87 - 1.33)	0.49

Table 4: A comparison of 30-day outcomes among young strokes with and without LVH, N=97

	LVH n=73 (%)	without LVH n= 24 (%)	Total n=97 (%)	p value
Mortality at 30 days	34 (46.6)	8 (33.3)	42 (43.3)	0.256
Functional independence (mRS 0 - 2)	8 (11.0)	4 (16.7)	12 (12.4)	0.461

mRS- modified Rankin Scale

Table 5: The sensitivity and specificity of the electrical voltage criteria in detecting LVH

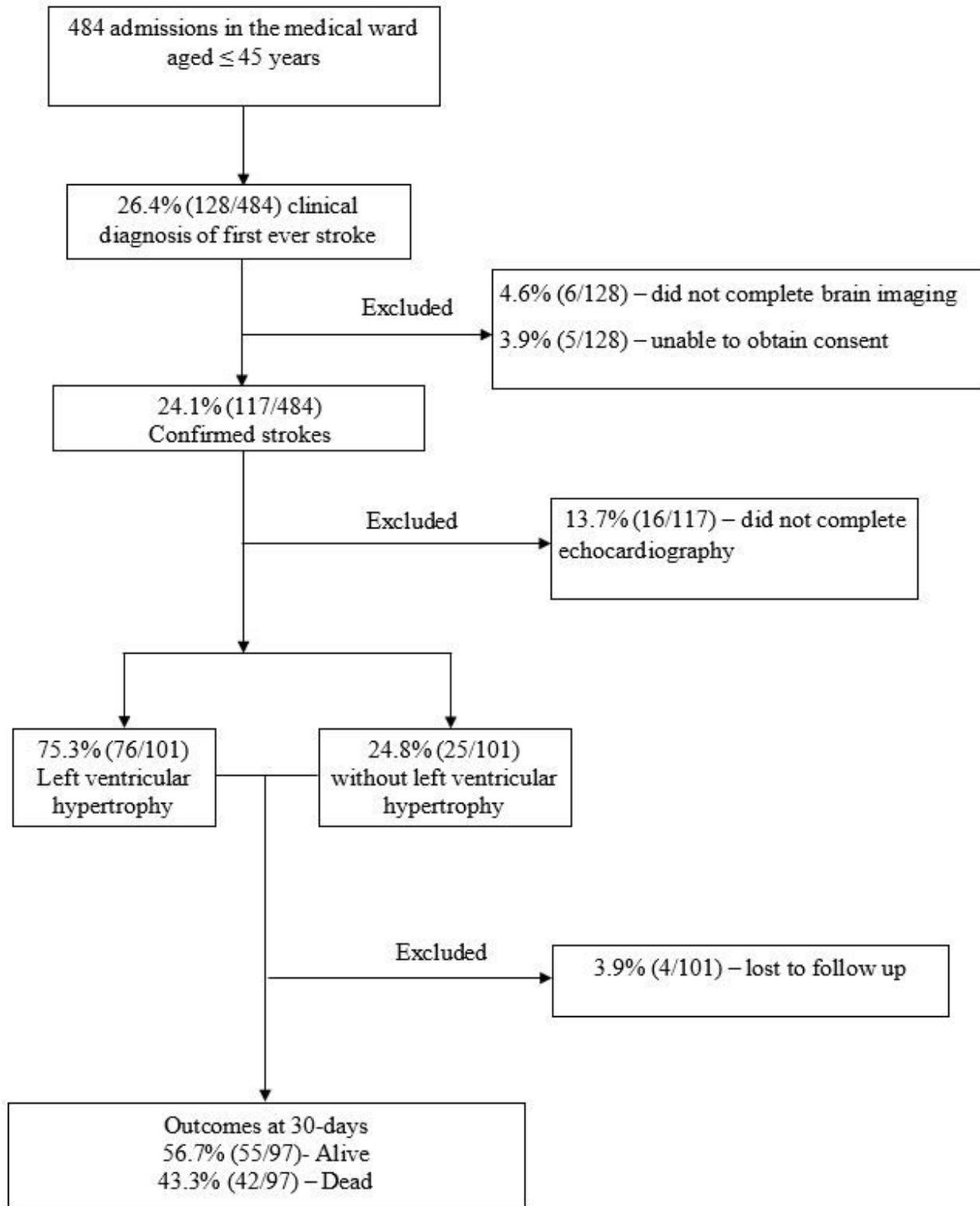|	Sokolow-Lyon criteria	Cornell criteria
True positive (n)	18	22
True negative (n)	18	12
False positive (n)	5	11
False negative (n)	50	46
Sensitivity (%) 95% CI	0.27 (0.17 - 0.39)	0.32 (0.22 - 0.45)
Specificity (%) 95% CI	0.78 (0.56 - 0.92)	0.52 (0.31 - 0.73)

Figures

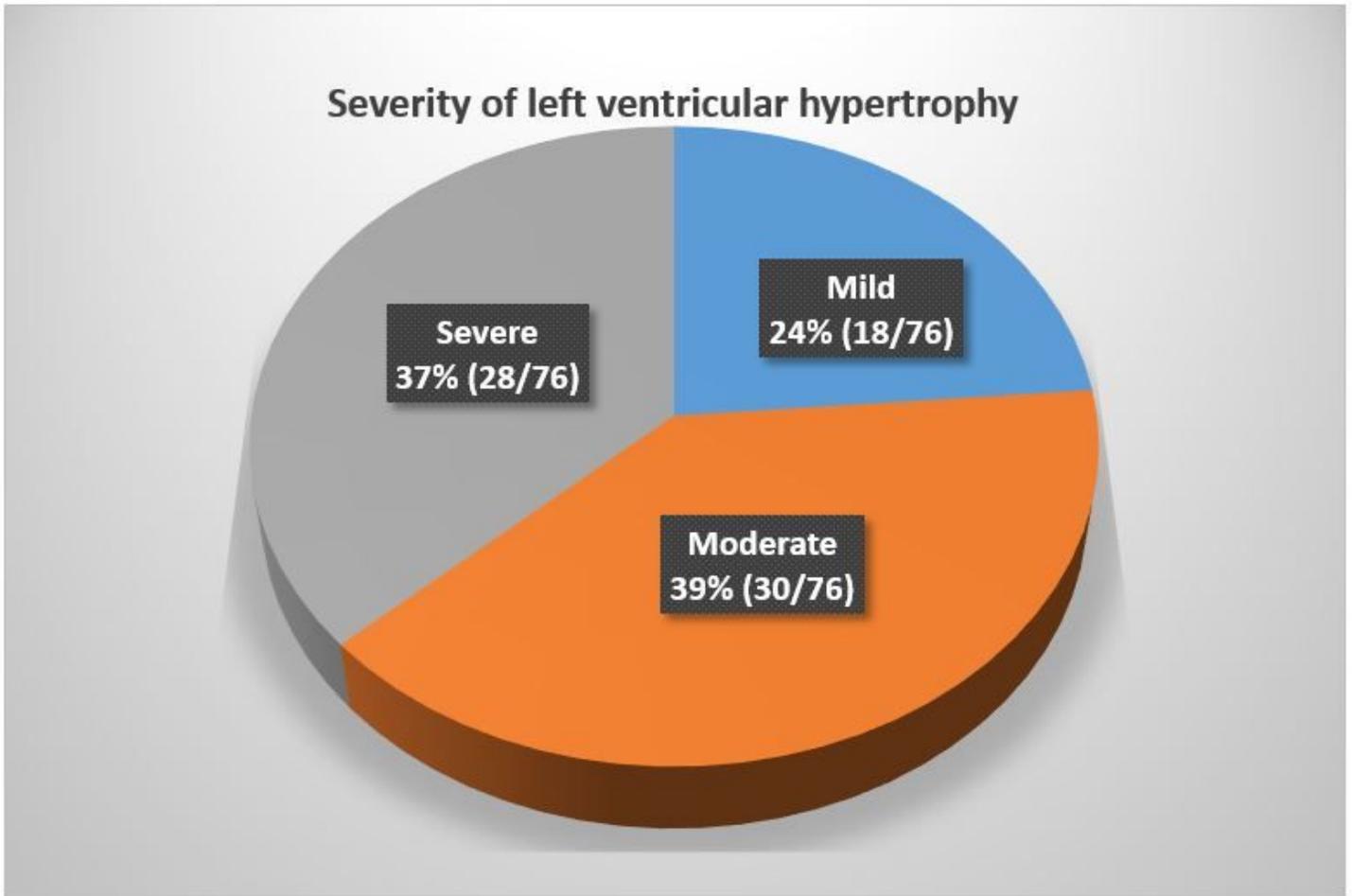**Figure 1**

Consort diagram showing the flow of participants

Figure 2

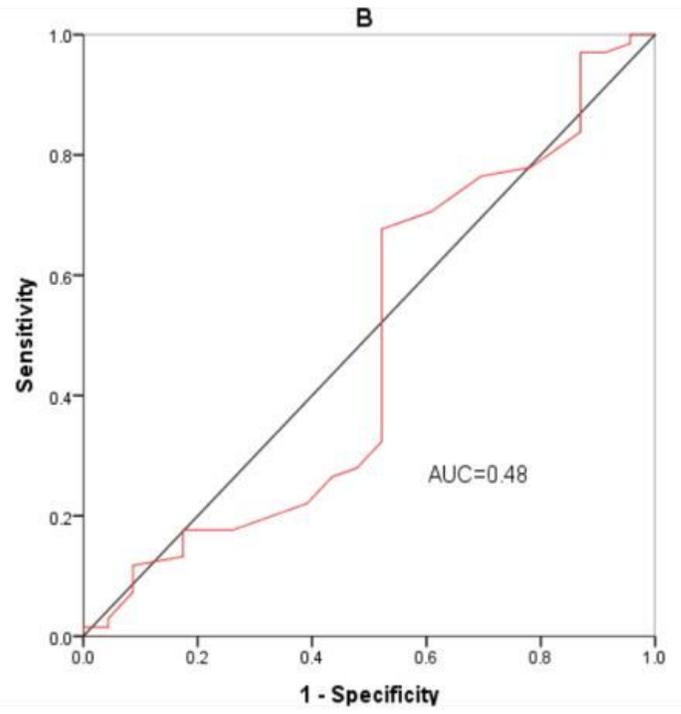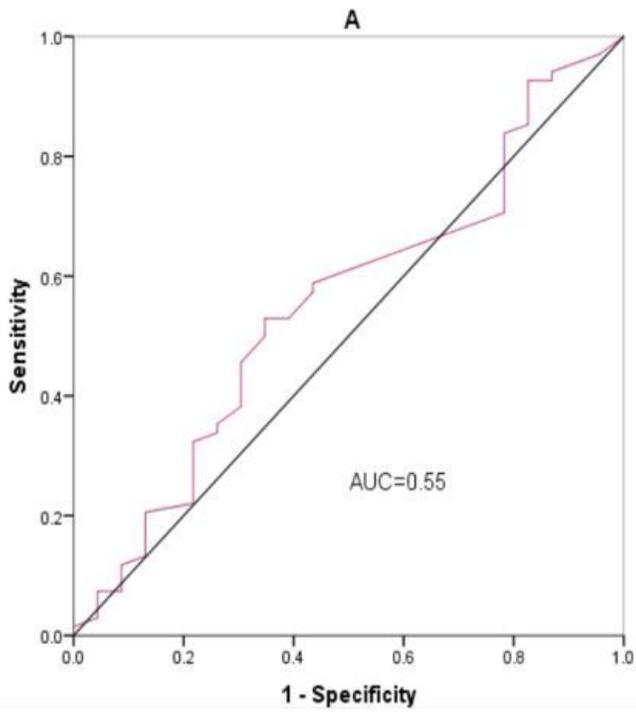Severity of LVH among young stroke participants, N=76

Figure 3

ROC and AUC of A Sokolow-Lyon criteria and B Cornell criteria for detecting LVH