The burden and outcome of stroke in young adults in a Tanzanian Tertiary Hospital: A Comparison with older Adults

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Abstract

Background: Stroke burden in young adults is growing and is associated with unique risk factors and devastating outcomes. We aimed at describing the magnitude, risk factors and outcomes of first ever stroke in young adults ≤45 years compared to older adults >45 years.

Methods: Participants were patients admitted with World Health Organization clinical criteria for stroke at a tertiary hospital in Tanzania. The National Institute of Health Stroke Scale and Modified Rankin Scale were used to assess for stroke severity and outcomes respectively. Kaplan-Meier analysis was used to estimate for survival.

Results: We enrolled 369 first ever stroke participants out of 1403 medical admissions over 8 months' duration. The overall stroke prevalence was 369 (26.3%) and was 123/484 {(25.4%) [95% CI 21.5% - 29.3%]} and 246/919 {(26.8%) [95% CI 23.9% - 29.6%]} for young and old respectively. Hemorrhagic stroke occurred in 47 (42.3%) vs 62 (27.2%) for the young and old respectively p=0.005. Factors associated with stroke in the young were: a new diagnosis of hypertension 33 (26.8%) vs 23 (9.3%) p<0.001, HIV infection 12 (9.8%) vs 7 (2.8%) p=0.005, use of hormonal contraception in females 33 (48.5%) vs 13 (9.4%) p<0.001, elevated serum low density lipoproteins 28 (27.7%) vs 29 (16.4%) p=0.024, hypercholesteremia 34 (31.2%) vs 40 (20.2%), p=0.031, sickle cell disease 11 (9.7%) vs 9 (4.2%) p=0.047 and thrombocytosis 12 (16.9%) vs 8 (5.6%) p=0.007. The median time for seeking health care was 2 days from stroke symptom onset. The overall 30-day fatality rate was 215 (61.3%) and 57 (49.1%) vs 158 (67.2%) in the young and old respectively.

Conclusions: There is a high prevalence of stroke in young adults that is coupled with a high 30day fatality rate. Screening and treatment of hypertension is key in prevention of stroke in the young.

Background

Stroke is a leading contributor to Disability Adjusted Life Years (DALYs), with low and middle income countries bearing the brunt of 4.85 million deaths and 91.4 million DALYs compared to 1.6 million and 21.5 million deaths and DALYs respectively in high income states (1). Stroke incidence increased steeply with age with 25% of strokes occurring in individuals below 65 years of age compared to 50% occurrence in individuals above 75 years (2). The population at risk for stroke has increased in low and middle income countries due to improved life expectancy mainly due to the control of HIV/AIDS (3). In Tanzania the life expectancy has increased from 49 years in 1995 to 66 years in 2015 (3) predisposing survivors to stroke.

The increase in the aging population coupled with lifestyle changes has resulted into an increased burden of diabetes and hypertension the main risk factors for stroke (4). In a three-year Tanzanian population based study conducted in 2004, the crude stroke incidence was 107.9 and 94.5 per 100,000 for urban and rural areas respectively and was 315.9 and 108.6 per 100,000 respectively after standardizing for age (5). This indicated that there was a higher stroke incidence in urban Tanzanian compared to stroke incidence

in the developed world. In this study the stroke incidence increased with age, however the incidence of stroke was higher in individuals below 44 years of age in urban settings 20.1 compared to 9.0 in rural settings (5).

Though stroke is common among the elderly, recent reports indicate a global rise in stroke incidence in young adults, with an increment of 36% from 35.1 per 10,000 to 47.6 per 10,000 between the year 2003 to 2012 among individuals aged 35 to 44 years (6). In the U.S there has also been a steep increase in stroke incidence in young adults ranging from 22 to 45 per 100,000 that occurred mainly in the black race (7). In SSA most of the available data on incidence of stroke in young adults was obtained more than decades ago that indicated a high incidence of 47 per 100,000 persons among those under 45 years (8). However, a more recent study in Nigeria reported a prevalence of 5.4% among those age between 35 to 44 years compared 25.6% among those aged between 55 to 64 years (9). Stroke at a young age paralyzes the nation's work force that is responsible for maintaining the nation's economy and population. Interestingly there has been an increase in risk of ubiquitous vascular factors that were previously thought to be scarce in the young population attributed to rapid health transitioning (10). Young adults also have other unique risk factors for stroke in addition to the traditional risk factors of diabetes and hypertension (10). The stroke incidence in the young is therefore expected to rise due to the rise in prevalence of hypertension and diabetes. We aimed at determining the magnitude of first ever stroke, the associated risk factors and short term outcomes at 30 days in young adults compared to the older adults in a tertiary hospital in Dar es Salaam, Tanzania.

Methods

Study Design and Population

This cohort study was conducted in a tertiary public teaching hospital at Muhimbili University of Health and Allied Science Academic Medical Center (MAMC), in Dar es Salaam, Tanzania. MAMC offers super-specialized medical care for all specialties and receives referrals from public and private hospitals from all over the country as well as walk in patients. We consecutively enrolled consenting participants who were admitted at MAMC with a clinical diagnosis of first ever stroke based on the World Health Organization (WHO) definition for stroke (11). Participants or their next of kin were required to provide written informed consent and had to be ≥ 18 years at the time of consent prior to enrollment. Study participants were prospectively enrolled between June 2018 to January 2019 and each participant was followed up to a total of 30 days from enrollment into the study.

Data collection

An interviewer based structured questionnaire was administered to all study participants or their caregivers if the participant was unable to communicate. The questionnaire captured sociodemographic information, smoking and alcohol consumption, history of hypertension, diabetes mellitus, cardiac

disease, and HIV infection. Other information collected included: use of medications for hypertension, diabetes, HIV, illicit drug use and use of hormonal contraception for females. The date of onset of stroke symptoms and date of arrival to the hospital was also recorded. Cigarette smoking and alcohol consumption was categorized as ever smoked and taken alcohol in life or never smoked or taken alcohol respectively. Current smokers/current alcohol consumers were defined as cigarette smoking/alcohol consumption within the last 12 months respectively.

All participants had their waist and hip circumference measured using a tape measure and recorded in centimeters. All participants were examined for radial pulse rate and rhythm, to detect for irregular pulses, and blood pressure (BP) measurements on the normal forearm and arm respectively. BP measurements was done using a standard digital BP machine AD Medical Inc. Three BP readings were collected spaced 5 minutes apart and an average BP was computed. Hypertension was defined as a systolic blood pressure (SBP) $\geq$ 140 mmHg or diastolic blood pressure (DBP) $\geq$ 90 mmHg. Precordial and neck carotid auscultation was performed using the stethoscope bell for mid-diastolic murmurs and carotid bruits respectively. Examination findings were recorded in a pre-specified case report forms.

We aseptically collected 15mls of venous blood from each study participant: 5mls were analyzed for random total cholesterol, triglycerides, low density and high density lipoproteins using BIO- SYSTEMS machine, 5 mls were analyzed for complete blood count using HEMOLYZER 3 PRO machine and 5mls were analyzed for sickling test. Sickling test was performed using sodium metabisulphite and slides were viewed using Olympus microscope.

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

Non-contrast brain computer tomography (NCCT) using GE Healthcare Optima or Magnetic Resonance Imaging (MRI) GE SIGNA CREATOR were performed to study participants at the MAMC radiology department and interpreted by a trained radiologist. Brain infarction was defined as a hypo dense area occupying a vascular territory and brain hemorrhage as a hyper dense lesion by NCCT. Infarction on MRI was defined as an area of iso/hypointensity on T1, high signal intensity on T2/Flair with high diffusion weighted imaging and low Apparent Diffusion Coefficient values and hemorrhage was defined as an area of variable T1/T2 signal based on age of stroke and a dark signal area in T2 sequence.

Transthoracic echocardiography (ECHO) using GE Medical Systems was performed by a trained cardiologist and interpretation was based on European Society of Cardiology/American Society of Echocardiography (12). Left ventricular muscle mass was assessed using a four chamber view at the end of diastole, a septal thickness > 10 mm and > 11 mm was considered LVH for females and males

respectively. Mitral Stenosis (MS) was defined as mitral valve area of > 1.5 cm^2 in short axis view and mean pressure gradient of < 5 mmHg using continuous Wave Doppler. A 12 lead electrocardiography (ECG) using Bionet machine was performed on the study participants to look for evidence of Atrial fibrillation.

Stroke severity was assessed using the National Institute of Health Stroke Scale (NIHSS) (11). A score of 1–4 was defined as minor stroke, 5–15 moderate stroke, 15–20 moderate to severe and 21–42 severe stroke. Stroke outcomes was defined as death or survival with disabilities using the Modified Rankin Scale (MRS) (11) at 24 hours, 72 hours, 7 days, 14 days and at 30 days from admission.

Data analysis

Data was transferred from the questionnaire and CRFs and entered into SPPS version 20.0 for analysis. The prevalence of stroke by age was presented as proportions and 95% confidence intervals. Continuous variables were summarized and presented as means and standard deviation (SD) or medians with Interquartile Range (IQR). Stroke risk factors by age were summarized as proportions and comparisons were made using Pearson's Chi square test or Fisher's exact test. Kaplan Meier analysis was applied to compare survival probabilities by age groups at 30 days. A p value of < 0.05 was considered to be of statistical significance.

Results

Prevalence of Stroke

There were 1,403 admissions in the medical ward; 484 (34.5%) were ≤ 45 years (young) and 919 (65.5%) were > 45 years (old) between June 2018 to January 2019, of these 430 (30.6%) participants met the WHO definition for stroke 131 (9.3%) young and 299 (21.3%) old. We recruited 369 participants with first ever stroke; 123 young and 246 old after excluding 61 (14.2%) participants. Reasons for exclusion included: inability to obtain consent 15 (3.5%), recurrent stroke 22 (7.4%), and stroke mimic 24 (5.5%) as summarized in consort diagram, Fig. 1. The prevalence of stroke in the young was 25.4% (123/484) and among the old was 26.8% (246/919) .

The overall mean age and SD was 57.4 ± 16 years and was 39.4 ± 5.2 years and 66.4 ± 11.3 years for the young and older stroke participants respectively. The baseline characteristics are summarized in Table 1, 729 (52%) were females with a significantly higher proportion of current alcohol consumers in the young compared to the old participants 23 (18.7%) vs 25 (10.2%) p = 0.022 and a lower proportion of young stroke participants were married compared to the old stroke participants 89 (72.4%) vs 244 (99.2%) p < 0.001.

Table 1: Baseline characteristics of the study participants with stroke

	Age groups			
	≤ 45 years n=123 (%)	> 45 years n=246 (%)	Total N= 369 (%)	p value
Female	68 (55.3)	138 (56.1)	206 (55.8)	0.882
Marital status				
Ever Married	89 (72.4)	244 (99.2)	333 (90.2)	<0.001
Never Married	34 (27.6)	2 (0.8)	36 (9.8)	
Residence				
Dar-es-Salaam	92 (74.8)	195 (79.3)	287 (77.8)	0.33
Health Insurance coverage				
Yes	37 (30.1)	65 (26.4)	102 (27.6)	0.459
Alcohol consumption				
Ever	28 (22.8)	45 (18.3)	73 (19.8)	0.309
Never	95 (77.2)	201 (81.7)	296 (80.2)	
Current	23 (18.7)	25 (10.2)	48 (13)	0.022
Cigarette Smoking				
Ever	8 (6.5)	17 (6.9)	25 (6.8)	0.884
Never	115 (93.5)	229 (93.1)	344 (93.2)	
Current	3 (2.4)	12 (4.9)	15 (4.1)	0.263

The overall median time from stroke onset to hospital arrival was 2 days IQR (1,4) and was 2 days IQR (1,3) and 2 days IQR (1,4) for the young and old stroke participants respectively. There were a total of 146 (39.6%), 55 (44.7%) young vs 91 (36.9%) old, p = 0.153 who arrived at the hospital within 24 hours from stroke symptoms, while 183 (49.6%) participants arrived at hospital between day 2 to 6 from onset of symptoms 57 (46.3%) vs 126 (51.2%) p = 0.326 in young and old respectively while 40 (10.8%) arrived 7 days after stroke symptoms.

Stroke subtypes

Brain imaging was performed on 339 (91.9%) participants, 30 (8.1%) participants did not undergo brain imaging: 20 (5.4%) participants died prior, 7 (5.7%) vs 13 (5.3%) in young and old, 6 (1.6%) participants were unable to pay for brain imaging, 3 (2.4%) vs 3 (1.2%) in young and old and in 4 (1.1%) there was

technical malfunction of the CT and MRI machines 2 (1.6%) in young and 2 (0.8%) in old. Hemorrhagic stroke occurred in 47 (42.3%) vs 62 (27.2%), p = 0.005 for the young and old stroke participants respectively, however the proportion of intracerebral hemorrhage was significantly higher in the old compared to the young stroke participants 67 (98.5%) vs 42 (89.4%), p = 0.041 respectively as summarized in Table 2.

Table 2: Brain imaging and stroke subtype in comparison by young and old

CT/MRI findings	Age groups			
	≤ 45 years	> 45 years	Total	p value
	n (%)	n (%)	N (%)	
Reasons for missing brain Images	12 (9.8)	18 (7.3)	30 (8.1)	0.419
Died prior to imaging	7 (5.7)	13 (5.3)	20 (5.4)	
Unable to pay for brain imaging	3 (2.4)	3 (1.2)	6 (1.6)	0.722
Technical malfunction	2 (1.6)	2 (0.8)	4 (1.1)	
Stroke sub-type				
Ischemic**	51 (45.9)	138 (60.5)	189 (55.8)	0.011
Hemorrhagic**	47 (42.3)	62 (27.2)	109 (32.2)	0.005
Mixed lesions **	0 (0.0)	6 (2.6)	6 (1.8)	0.085
Normal **	13 (11.7)	22 (9.6)	35 (10.3)	0.558
Vessel involved (ischemic/mixed)				
Major vessel disease	21 (41.2)	80 (55.6)	101 (51.8)	0.077
Small vessel disease	21 (41.2)	48 (33.3)	69 (35.4)	0.314
Mixed vessel disease	9 (17.6)	16 (11.1)	25 (12.8)	0.23
Area of Hemorrhage (hemorrhage/mixed)				
Intracerebral	42 (89.4)	67 (98.5)	109 (94.8)	0.041
Intraventricular	2 (4.3)	0 (0.0)	2 (1.7)	0.165
Subarachnoid	3 (6.4)	1 (1.5)	4 (3.5)	0.303

** Brain imaging performed on 339 participants, 111 were ≤ 45 years and 228 were > 45 years

Stroke risk factors

Table 3 summarizes factors associated with stroke in the young compared to the old: a new diagnosis of hypertension 33 (26.8%) vs 23 (9.3%) p < 0.001, HIV infection 12 (9.8%) vs 7 (2.8%) p = 0.005, female use

of hormonal contraception 33 (48.5%) vs 13 (9.4%) p < 0.001, illicit drug use 5 (4.1%) vs 2 (0.8%) p < 0.044. Mitral stenosis was unique to the young 4 (4%) vs 0 (0%) p = 0.013. Other factors in the young were sickle cell disease 11(9.7%) vs 9 (4.2%) p = 0.047, elevated low density lipoproteins 28 (27.7%) vs 29 (16.4%), p = 0.024, hypercholesteremia 34 (31.2%) vs 40 (20.2%), p = 0.031 and thrombocytosis 12 (16.9%) vs 8 (5.6%), p = 0.007.

Table 3
Risk factors for stroke by age groups

Risk factors	Age groups			
	≤ 45 years	> 45 years	Total	p value
	n (%)	n (%)	N (%)	
Hypertension				
Known	78 (63.4)	207 (84.1)	285 (77.2)	< 0.001
New diagnosis	33 (26.8)	23 (9.3)	56 (15.2)	< 0.001
On treatment	30 (38.5)	88 (42.5)	118 (41.4)	0.536
Diabetes				
Known	17 (13.8)	47 (19.1)	64 (17.3)	0.206
New diagnosis	2 (1.6)	1 (0.4)	3 (0.81)	0.259
On treatment	11 (64.7)	20 (42.6)	31 (48.4)	0.117
HIV infection				
Known	12 (9.8)	7 (2.8)	19 (5.1)	0.005
New diagnosis	2 (1.6)	5 (2)	7 (1.9)	1
On treatment	11 (91.7)	7 (100)	18 (94.7)	1
Hormonal contraception	33 (48.5)	13 (9.4)	46 (22.3)	< 0.001
Illicit drugs	5 (4.1)	2 (0.8)	7 (1.9)	0.044
Family history of hypertension	42 (34.1)	83 (33.7)	125 (33.9)	0.938
Family history of diabetes	11 (8.9)	33 (13.4)	44 (11.9)	0.211
Family history of sudden death	8 (6.5)	11 (4.5)	19 (5.1)	0.405
Irregular pulse	3 (2.4)	25 (10.2)	28 (7.6)	0.008
Mid diastolic murmur	4 (3.3)	0 (0)	4 (1.1)	0.012
Increased waist- hip ratio	95 (77.2)	197 (80.1)	292 (79.1)	0.526
Hypercholesteremia	34 (31.2)	40 (20.2)	74 (24.1)	0.031
Elevated low density lipoproteins	28 (27.7)	29 (16.4)	57 (20.5)	0.024
Sickle cell	11 (9.7)	9 (4.2)	20 (6.1)	0.047
Thrombocytosis	12 (16.9)	8 (5.6)	20 (9.3)	0.007

	Age groups			
ECG findings				
Atrial fibrillation	3 (3)	18 (9)	21 (7)	0.059
ECHO findings				
Mitral stenosis	4 (4)	0 (0)	4 (1.4)	0.013
Left ventricular hypertrophy	76 (76)	173 (90.6)	249 (85.6)	0.001

Stroke severity

A total of 207 (56.1%) participants had severe stroke on admission, 54 (43.9%) vs 153 (62.2%), p < 0.001 for the young and old respectively, moderate stroke occurred in 44, (35.8%) vs 60 (24.4%), p = 0.022 for the young and old respectively.

Stroke fatality

The overall fatality rate at 30 days was 215 (61.3%) and was 57 (49.1%) vs 158 (67.2%), p = 0.001 in the young and old respectively. Fatality was highest within the first week of hospital admission as summarized in Fig. 2, Kaplan Meier curve for 30-day survival in young and old stroke participants. There were 18 (4.9%) participants who were lost to follow up following discharge from hospital 7 (5.7%) young and 11 (4.5%) old, p = 0.608.

Discussion

There was a high first ever stroke prevalence in young adults, with similar rates observed to that of the older population admitted at MAMC. These findings are quite alarming as stroke was initially thought to be a disease of the elderly with incidence rates expected to increase with age increment. However, the Global Burden of Disease report stated that stroke should no longer be regarded as the disease of the old as it has the same potential of affecting the young (13). This high stroke burden in the young calls for urgent interventions that should address risk factors as approximately 50% of the Tanzanian population comprises of individuals between 15 to 54 years who are the nation's work force (14).

The high stroke prevalence in the young observed in our study was attributed to several factors such as hypertension. Hypertension is a known risk factor for stroke as was observed in more than two-thirds of the study participants, similar to what was has been reported (15). Surprisingly, only 41.4% of the stroke participants who were known to be hypertensive were on regular treatment for hypertension. Noteworthy, is the fact that a quarter of the young stroke participants were newly diagnosed hypertensives at hospital admission. These high rates of new hypertension observed in younger adults should be interpreted with caution due to the initial blood pressure surge that occurs as a result of physiological auto regulatory mechanisms following an acute stroke (16). This indeed calls for awareness and regular screening for hypertension as has been observed in four SSA countries whereby 45% of all strokes could be prevented

by simply measuring and controlling blood pressure (17). There is a need to for further study on etiologies for hypertension among young adults in Tanzania.

We observed a significant contribution of hemorrhagic stroke in the young. In India hemorrhagic stroke secondary to hypertension was common in the young (18). Hypertension causes lipohyalinosis and micro-atheroma that results into rupture of cerebral blood vessels (19).

Mitral stenosis was a unique risk factor for stroke in the young mainly due to atrial fibrillation with consequent thrombus formation that eventually dislodges to the brain (20). Prevention of rheumatic heart disease in the young is an important strategy, use of anticoagulant therapy to prevent thrombus formation and valvular repair is warranted for patients with mitral stenosis.

HIV infection was common in the young. HIV itself or with other opportunistic infections results into vasculitis, cardio-embolism and coagulopathy (21). Likewise, the use of certain antiretroviral therapy (ARVs) for HIV has been known to cause dyslipidemia that predisposes to stroke (22). ARVs prolongs patient survival thus predisposing individuals to traditional risk factors for stroke.

The use of oral contraceptives among females with stroke was another factor observed in this study. Combined oral contraceptives increases the likelihood of ischemic stroke by causing thrombosis especially in women who smoke and have hypercholesteremia (23). There a need to screen women with preexisting risks prior to prescribing oral contraceptive pills.

Sickle cell disease (SCD) was another risk factor observed among the young in our study as described previously especially in individuals below 35 years (24). In this study we did not look into specific sickle cell genotypes however we propose regular follow up of SCD patients with use of drugs such as hydroxyurea so as to prevent cerebrovascular complications.

A significant proportion of young adults had hypercholesteremia and increased LDL. Dyslipidemia is a known risk factor for stroke in young which adversely affects arteries by promoting atherosclerosis which in turn impairs blood pressure regulation predisposing individuals to hypertension (18). Similarly, factors such as smoking, alcohol consumption and diabetes mellitus which were observed in current study are also known to exacerbate the likelihood of dyslipidemia. We thus recommend screening for dyslipidemia in young adults and life style modifications.

There was an alarming overall high fatality rate of 61% at 30 days, with high rates in both the young and old. The WHO report for 2017, indicated that stroke is the 6th top cause of death in Tanzania, however mortality data for stroke in the young was lacking (25). This study has shed some light on the contribution of stroke deaths among young adults. Furthermore, the current study has a high fatality compared to what was reported two years ago in a tertiary hospital that reported a fatality rate of 33.3% (26). Our study did not look into early predictors of fatality, however we observed that participants delayed in seeking medical care and majority had severe stroke on admission these could have been some of the factors that might have contributed to the high fatality rates. Time is key for intervening

following stroke and delays leave minimal opportunities for any neurovascular based interventions, consequently living health care providers with limited conservative management (27).

We followed the study participants for only 30 days' post stroke for outcomes, we recommend long term follow up of the young stroke survivors.

Conclusions

There is a high prevalence of stroke in young adults that is coupled with a high 30-day fatality rate. Screening and management of hypertension is crucial in prevention of stroke among the young. Raising awareness of stroke is an important preventive method and could reduce fatality.

Abbreviations

AF
Atrial Fibrillation
ADC
Apparent Diffusion Coefficient
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
RHD
Rheumatic Heart Disease
SSA
Sub Saharan Africa
WHO
World Health Organization

Declarations

Ethical approval and consent to participate: Ethical clearance was obtained from Muhimbili University of Health and Allied Sciences Institutional review board approval number DA.287/298/01A/. Written

informed consent to take part in the study and for HIV testing was obtained from all study participants or their next of kin prior to study enrollment. All patients were offered standard of care following diagnosis.

Consent for publication: Participants gave consent for publication that was requested for during the informed consent process.

Availability of data and materials: Dataset used for analysis in this study is not publicly available to maintain participant confidentiality. Data are however available from the corresponding author on reasonable request.

Competing interests: We declare no conflict of interest.

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Authors contributions: SSM and PM conceptualized and designed the study, performed data analysis, interpreted the results and wrote the manuscript. SSM and KK collected data, KK performed the ECHOs.

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Figures
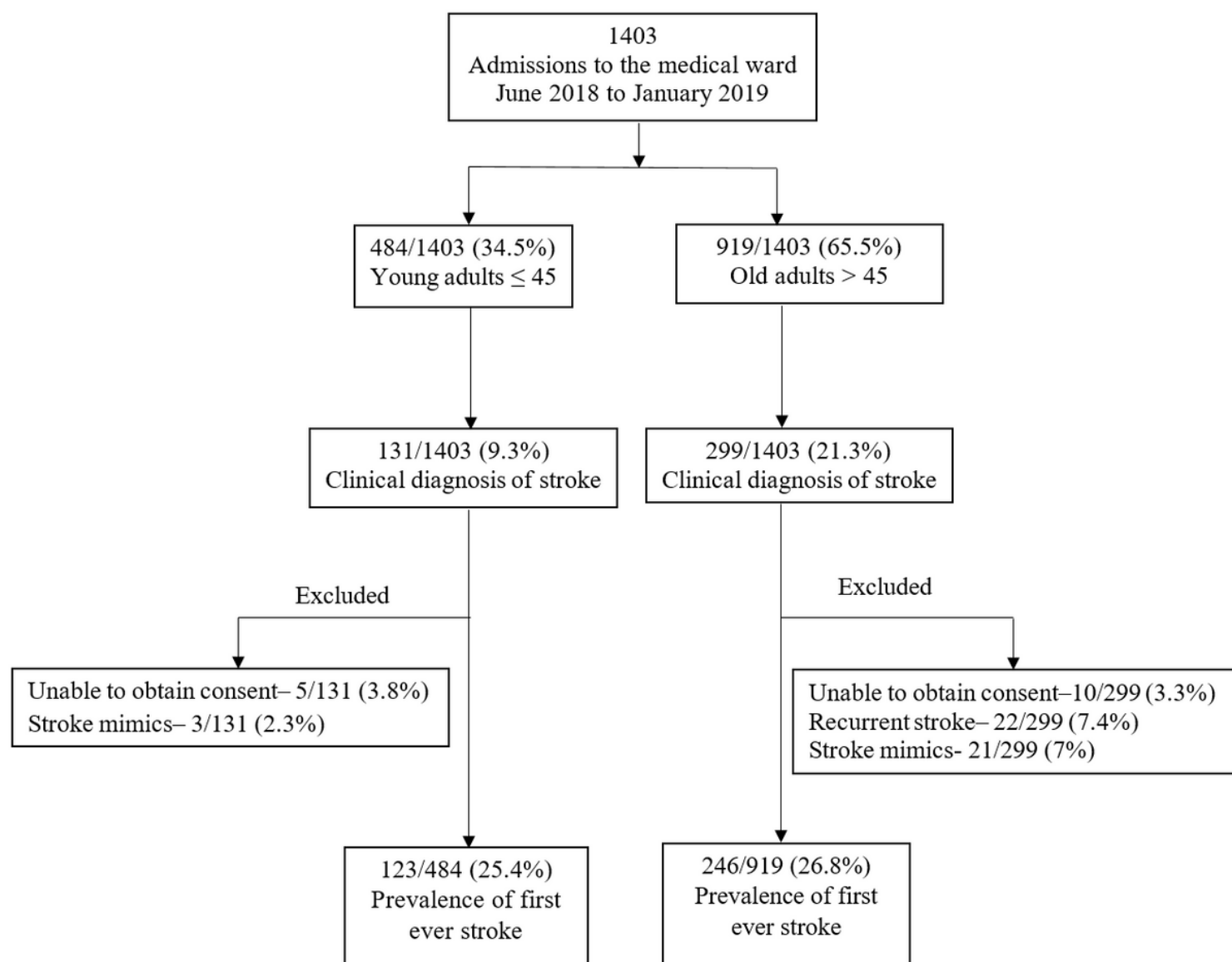
Figure 1

Consort diagram showing the flow of participants
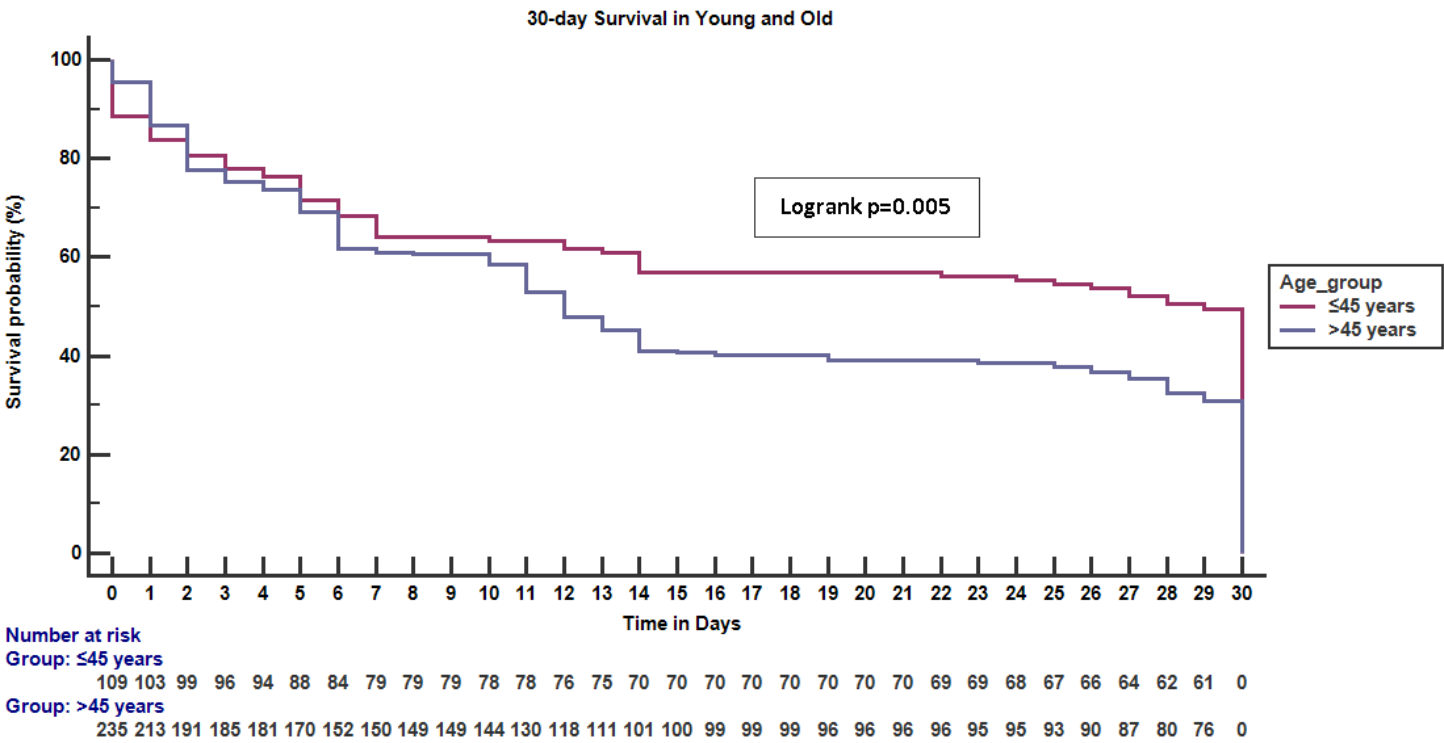
Figure 2

Kaplan Meier survival curve for 30-day survival in young and old stroke participants