

Knowledge of Risk Factors and Warning Signs of Stroke Among Patients with Heart Disease at Tikur Anbessa Specialized Hospital

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Background: Stroke is a leading cause of mortality and disability worldwide and the economic costs of treatment and post-stroke care are extensive. The inability to identify stroke warning signs accurately is an important cause of delay in seeking medical attention, leading to potential ineligibility for acute intervention and which leads to secondary complications.

Purpose: To identify cardiac patients' knowledge of stroke risk factors and warning signs.

Patients and Methods: The institutional based cross-sectional study design was employed. Participants were selected using systematic random sampling. Close-ended questionnaires were pre-tested and validated for consistency before data collection. Then after data collection, data were checked and entered into Epi-data 4.6. Finally, the cleaned data were exported to SPSS version 25 for analysis. Statistical analysis using binary logistic regression was done and Predictors with a p-value of <0.05 were considered statistically significant.

Results: A total of 227 patients were included in the study, of which 140 (61.7%) of them identified physical inactivity, followed by hypertension 126 (55.5%) as stroke risk factor while 15.4% of them did not know any risk factor of stroke. Amongst the study participants, 45.81% of them had adequate knowledge of stroke risk factors. Regarding stroke warning signs the most identified sign was sudden unilateral weakness 142 (62.6%) while 46 (20.26%) of them did not know at least one warning sign of a stroke. Based on multivariable logistic regression analysis, higher education level AOR 3.05 (95% CI 1.62–5.74) and Urban residence area AOR 2.07 (95% CI 1.05–4.1) were significantly associated with knowledge of stroke risk factors with p-value<0.05.

Conclusion: Study participants had inadequate knowledge of stroke risk factors and warning signs. Educational status and information about stroke are significantly associated with adequate knowledge of stroke risk factors, raising stroke awareness is the mainstay to reduce stroke burden.

Keywords: knowledge, risk factors, stroke, a warning sign

Introduction

Stroke is a leading cause of mortality and disability worldwide and the economic costs of treatment and post-stroke care are substantial.¹ The inability to identify stroke warning signs accurately is an important cause of delay in seeking medical attention, leading to potential ineligibility for prompt intervention.² Prevention of main modifiable risk factors of cardiovascular diseases (CVD) such as hypertension, diabetes mellitus, physical inactivity, smoking, and obesity through effective prevention strategies consequently reduces disability and mortality occurs due to stroke.^{3–5}

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World stroke association practices warning signs of stroke using the acronym FAST (face, arm, speech, time) message campaign, to explain knowing the signs of stroke and getting treatment quickly saves lives and improves recovery even though the stroke burden is increasing globally.^{3,4,6,7}

A good functional outcome from a stroke begins when the public recognizes stroke warning signs.^{8,9} However, the public's knowledge of stroke warning signs remains poor.^{6,10} Evidence from studies in developed and developing countries shows that respondents' recognition of any of the established stroke risk factors or warning signs is generally less than 50%.^{11–13} A pre-hospital delay is shortened through advanced notification of stroke warning signs and increases the use of the intravenous recombinant tissue-type plasminogen activator.^{1,3,11}

The overall stroke burden has increased globally, due to poor community knowledge of stroke risk factors and its warning signs.^{14–16} Necessary intervention should be carried out to decrease stroke other communicable disease burdens, otherwise, the total death from it is anticipated to increase further 17% over the next first decade.^{12,13}

The 2014 WHO report states that stroke accounted for 4.71% of total deaths and the leading cause of disability (6458 age-standardized DALYs per 100,000) in Ethiopia.^{17,18} This is due to delayed presentation and the increasing burden of stroke risk factors.^{19–22}

Given the already huge and fast-increasing burden of stroke which threatens worldwide sustainability, governments of all countries should develop and implement an emergency action plan addressing the primary prevention of NCDs, to tackle unhealthy behaviors that increase the risk of stroke.^{4,23–25} So, the main objective of this study is to show the gap between unhealthy behaviors that increase the occurrence of stroke and reduce the pre-hospital delay that occurs due to a lack of awareness on recognition of stroke warning sign and its associated factors.

Patients and Methods

Study Design and Setting

An institutional-based cross-sectional study design was conducted at Tikur Anbessa specialized hospital from March 15 to April 25, 2020. Tikur Anbessa specialized hospital is located in the capital city of Ethiopia. It is the largest teaching hospital in the country, which provides health care services to over 700,000 patients per year and

serves as a training and teaching center for health programs.^{25,26}

Study Population

Patients with heart disease who visit Tikur Anbessa specialized hospital cardiac clinic for follow-up during the study period.

Eligibility Criteria

Cardiac patients aged ≥ 18 years who visit TASH outpatient cardiac clinic were included in the study, while critically ill and psychiatric patients were excluded.

Sample Size Determination and Sampling Procedure

The required sample size was determined using the single population proportion formula with the assumption of 95% confidence level, 5% margin of error, and 18.3% proportion of hypertensive patients who have good knowledge of stroke risk factors.¹³ The initial sample size (n_i) = $(Z\alpha/2)^2 p(1-p)/d^2 = 230$ was adjusted using a correction formula for a total of 2380 outpatient cardiac patients who were on follow-up were eligible for the study based on inclusion criteria from the follow-up chart was taken. Finally, a total of 231 cardiac patients were targeted for the study after the addition of a 10% non-response rate. Patients' record order which was listed in follow-up appointment was used as a sampling frame, Study participant was selected by systematic random sampling technique a using list of record orders in the follow-up chart with sampling interval (k) = N/nf ; $2380/231=10$; then, in every 10 intervals, participants selected until reaching the total sample size and the first participant was selected by lottery method.

Data Collection Tool and Procedure

Close-ended standard stroke awareness questionnaires were adapted which contain socio-demographic characteristics, stroke risk factors, and stroke warning signs used in the previous literature that were used.^{9,13,27,28} The patients' knowledge of stroke risk factors and warning signs were categorized based on the number of correct answers of stroke warning signs and warning signs, respectively. Participants who selected the yes option from each listed risk factors and warning signs of stroke were considered correct. Therefore, participants who identified >3 risk factors or warning signs of stroke were categorized as having good knowledge of stroke risk factors or

its warning signs, respectively.^{29,30} Face to face interview technique was conducted by trained four BSc nurses.

Data Quality Assurance

The questionnaire was pretested on 5% of the sample size on patients with heart disease who are on follow-up at Saint Paul hospital. During the pre-test, the questionnaire was assessed for its understandability, and reliability statistics were computed with Cronbach's alpha of 0.87. Questionnaires were translated to Amharic and Afan Oromo languages by language experts then back to English during data analysis. The training was given for data collectors and the supervisor provided on-site close supervision during data collection.

Data Processing and Analysis

Data were checked for completeness and entered into Epi-data entry client version 4.6. Then, it was exported to and analyzed using SPSS version 25.0. Descriptive statistics were computed to summarize categorical variables of patients' characteristics. The statistical analysis using binary logistic regression was done to determine candidate variables for multivariable logistic regression at p-value <0.25. Then, variables having p-value <0.05 at 95% CI in multivariable logistic regression were considered statistically significant.

Ethical Consideration

The letter of permission was approved by the Addis Ababa University College of health science department of emergency medicine ethical review committee with Ref No: EM/SM/350/2012 and was given to Tikur Anbessa specialized hospital administrator and this study was conducted in accordance with Helsinki declaration. Written informed consent was taken from each participant. Data collectors explained the objectives and their right to refuse and discontinue the data collection.

Results

A total of 227 participants were included in the study giving a response rate of 98.3%. The mean age of respondents was 46.2 ± 17.9 . Regarding the sex of participants more than half 132 (58.1%) were females, and around two-thirds (69.2%) of patients were married. Concerning educational status, 64 (28.2%) of them learned up to elementary school. Most of the participants' residence area was urban which accounts for 154 (67.8%) (Table 1).

Knowledge of Stroke Risk Factors

The most identified stroke risk factor by respondents was physical inactivity 140 (61.7%) of them followed by hypertension 126 (55.5%), whereas only less than half (42.7%) of study participants identified diabetes mellitus as a risk factor of stroke (Table 2). Among the study participants around 15.4% of them did not know any risk factor of stroke, while 16.3% of them identified five risk factors of stroke followed by 15.9% of the respondents identified all (6) listed risk factors (Figure 1). Among the study participants, less than half (45.8%) of them had adequate knowledge of stroke risk factors.

Knowledge of Stroke Warning Signs

A majority, 142 (62.6%) of the study participants identified sudden unilateral numbness/weakness of the face, arm, or leg, followed by sudden trouble with walking, loss of balance 137 (60.4%) as the warning signs of a stroke, whereas sudden trouble with seeing in one or both eyes is least, 93 (41.0%), known warning signs of stroke among study respondents (Table 3). Among the study participants, 46 (20.3%) of them did not know at least one warning sign of stroke, while 49 (21.1%) of the respondents recall 5 warning signs of a stroke (Figure 2). Only Less than half (42.7%) of study respondents had adequate knowledge about stroke warning signs.

Factors Associated with Stroke Risk Factors and Warning Signs

In the bivariate logistic regression, age, educational level, occupation, residence area, hearing about stroke, and knowing somebody with stroke were found to have a significant association with knowledge of stroke risk factors and warning signs (Table 4).

In the multivariable logistic regression educational level, residence area, and knowing somebody with stroke were significantly associated with knowledge of stroke risk factors and warning signs having a P-value of <0.05. The odds of having adequate knowledge of stroke risk factors among those who had a higher educational level was 3.05 times (AOR 3.05; 95% CI 1.62–5.74, P=0.005) than participants who had educated less than high school. Urban residence area was 2.07 times (AOR 2.07; 95% CI 1.05–4.1, P=0.036) more likely to have adequate knowledge of stroke risk factors than participants who live in the rural area. Furthermore, knowing somebody with stroke was 2.67 times (AOR 2.67; 95% CI 1.29–5.55, P=0.008) more likely to have adequate

Table 1 Socio-Demographic Characteristics of Patients with Heart Disease Who are on Follow-Up at Tikur Anbessa Hospital, 2020 (n=227)

Variables			Frequency	Percent
Age	Mean \pm SD in years	46.2 \pm 17.9		
	18–44		104	45.8
	45–64		79	34.8
	≥ 65		44	19.4
Clinical profile of patients	Valvular heart disease		26	11.5
	Heart failure		19	8.4
	Hypertension		73	32.1
	Dyslipidemia		14	6.2
	Heart rhythm disorder		11	4.8
	Congenital heart defects		23	10.1
	Heart infections		24	10.6
	Ischemic heart disease		37	16.3
Sex	Male		95	41.9
	Female		132	58.1
Marital status	Married		157	69.2
	Single		43	18.9
	Divorced		16	7.0
	Widowed		11	4.8
Educational status	Illiterate		53	23.3
	Elementary		64	28.2
	High school/preparatory		62	27.3
	College and above		48	21.1
Occupation	Farmer		34	15.0
	Merchant		71	31.3
	Government employee		32	14.1
	Housewife		54	23.8
	Student		17	7.5
	Other*		19	8.4
Monthly income in ETB	≤ 5000		27	11.9
	> 5000		200	88.1
Residence area	Urban		154	67.8
	Rural		73	32.2

Note: *Daily laborer, jobless, pensioner.

knowledge of stroke risk factors than others who do not know somebody with stroke. Concerning knowledge of warning signs, the odds of having adequate knowledge of stroke warning signs were 2.95 times (AOR 2.95; 95% CI 1.28–6.83, $P=0.107$) in participants who had higher educational level than those who had educational level less than high school, besides to this know somebody with stroke was 10.85 times (AOR 10.85; 95% CI 4.38–26.90, $P=0.000$) more likely to have adequate knowledge of stroke warning signs than others who not know somebody with stroke (Table 5).

Table 2 Risk Factors of Stroke Identified by Patients with Heart Disease Who are on Follow-Up at Tikur Anbessa Hospital, 2020 (n=227)

Variables		Frequency	Percent
Hypertension	Yes	126	55.5
	No	38	16.7
	I do not know	63	27.8
Obesity	Yes	123	54.2
	No	52	22.9
	I do not know	52	22.9
Excessive alcohol intake	Yes	122	53.7
	No	54	23.8
	I do not know	51	22.5
Diabetes mellitus	Yes	97	42.7
	No	49	21.6
	I do not know	81	35.7
Physical inactivity	Yes	140	61.7
	No	30	13.2
	I do not know	57	25.1
Smoking	Yes	108	47.6
	No	49	21.6
	I do not know	70	30.8

Discussion

To tackle global invisible socio-economic burdens of stroke; prevention is the mainstay both in low- and high-income countries, so this study aims to identify participants' awareness of stroke risk factors and its warning signs.

Most study participants identified physical inactivity 140 (61.7%) of them as a risk factor of stroke followed by hypertension 126 (55.5%), while the least known risk factor of stroke was diabetes mellitus 97 (42.7%). This study finding is relatively consistent with a study conducted in Pakistan that shows a majority (63.5%) of patients identified hypertension as a risk factor for stroke.²⁹ Besides this study conducted in Lebanon reveals 188 (48.2%) of them had identified hypertension as stroke risk factors.³¹ And also, relatively consistent with a study conducted in Nigeria that reveals the most recalled stroke risk factors were hypertension 71 (45.4%) and diabetes 72 (42.2%).²⁷ This might be due to the study participants with an identical study design. This study finding was, in contrast, to a study conducted in Spain that shows that 22.68% of the study participants identified hypertension as a stroke risk factor.³² This inconsistency might be due to the study

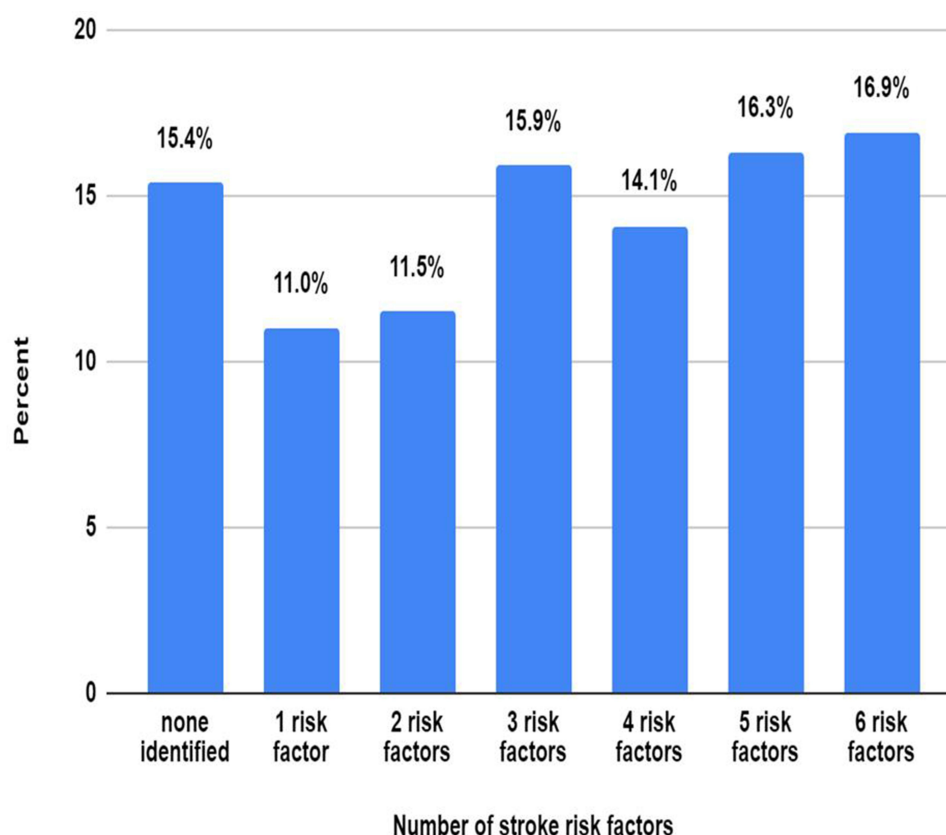


Figure 1 Number of stroke risk factors identified by patients with heart disease who were on follow-up at TASH, 2020.

being conducted on admitted stroke patients, stroke may affect the intellectual ability of the study participants. Our findings were also inconsistent with studies conducted in Korea and the USA.^{30,33} This might be due to the health care information access gap and socioeconomic status difference between low- and high-income countries. However, this study finding was higher than the study finding conducted in Ethiopia.¹³ This gap might be due to increasing health care awareness and a difference in the study site and residency of participants within the country. Among the study participants, around 15.4% of them did not know any risk factor of stroke, while 15.9% of them identified all listed risk factors. Besides this less than half (45.8%) of them had adequate knowledge of stroke risk factors. This study finding is relatively consistent with the study conducted in Thailand that shows a quarter of patients (25%) could not name any risk factors for stroke.²⁸ This study was also relatively similar to a study conducted at Benin that reveals 82 (56.9%) of participants had good knowledge of stroke risk factors.²⁷ The similarity might be due to studies that were conducted on similar types of study participants. In contrast to these studies,

studies conducted in the USA and Korea show participants knowledge of correct stroke risk factors >3 accounts 117 (71.8%) and more than 60% of the participants recognized over-all the risk factors, respectively.^{30,33} This shows a higher number of study participants had adequate knowledge of stroke risk factors. The possible justification for it was due to rising health care awareness in such study areas, the difference in socioeconomic status, and study participants' selection method.

Regarding knowledge of stroke warnings sign, sudden unilateral weakness of the extremities 142 (62.6%), sudden trouble with walking or loss of balance were and 137 (60.4%) were the most commonly identified warning signs, whereas 46 (20.3%) of them had not mentioned any warning signs of stroke and only Less than half (42.7%) of study respondents had adequate knowledge of stroke warning signs. This study finding was relatively consistent with studies conducted in Lebanon that show around a third (31.8%) of the study participants could not recall any stroke symptom.³¹ Additionally, there was a relative similarity with a study conducted in Nigeria that shows study participants identified the weakness of

Table 3 Warning Signs of Stroke Identified by Patients with Heart Disease Who Were on Follow-Up at TASH, 2020 (n=227)

Variables		Frequency	Percent
Sudden unilateral numbness/weakness of the face, arm, or leg	Yes	142	62.6
	No	39	17.2
	I do not know	46	20.3
Sudden trouble with walking, loss of balance	Yes	137	60.4
	No	49	21.6
	I do not know	41	18.1
Sudden trouble with speaking or communication problem	Yes	115	50.7
	No	57	25.1
	I do not know	55	24.2
Sudden severe headache with no known causes	Yes	125	55.1
	No	49	21.6
	I do not know	53	23.3
Sudden trouble with seeing in one or both eyes	Yes	93	41.0
	No	76	33.5
	I do not know	58	25.6

part of body 52 (36.1%) and 79 (54.9%) of study participants had good symptom knowledge.²⁷ The possible reason for this similarity might be due to identical study participants' selection method, sample size calculation and study design. However, a study conducted in Thailand revealed that 19 (13.6%) of participants could not identify any warning signs and only 6(4.3%) of them identified sudden unilateral numbness of extremities,²⁸ which shows lower than our study finding, that might

occur due to researchers used an open-ended questionnaire to carry out the study. Furthermore, this study findings were higher than a study conducted in Ethiopia, which shows 217 (77.3%) of participants did not identify any warning signs of a stroke, 2 (0.7%) identified 3 warning signs and (35.9%) of them recalled sudden weakness or paralysis on one side of the body.¹³ The inconsistencies might be due to health care information outcome in response time and that study was conducted at the peripheral region of the country that might result in healthcare information access gap.

In the multivariable logistic regression analysis, those who had higher education level was three times more likely to had adequate knowledge of risk factors (AOR 3.05; 95% CI 1.62–5.74), the odds of having adequate knowledge in urban residence area was 2.07 times (AOR 2.07; 95% CI 1.05–4.1) more likely than rural area residents. Furthermore, those who know somebody with stroke were 2.67 times (AOR 2.67; 95% CI 1.29–5.55) more likely to have adequate knowledge of stroke risk factors. This study finding was similar to a study conducted in Nigeria that reveals higher educational level (OR 11.3, 95% CI, 2.88–44.6, $P < 0.001$), are found to be significant predictors of good knowledge of stroke risk factors.²⁷ Besides this study conducted in Central Pennsylvania shows that a high level of education increases odds of recognition of >3 correct stroke risk factors (0.21; 95% CI, 0.09–0.61) with additional Knowing anyone with stroke was associated with knowledge of stroke risk factor.³⁰ Also, our study finding was consistent with a study conducted in Spain and Ethiopia that shows

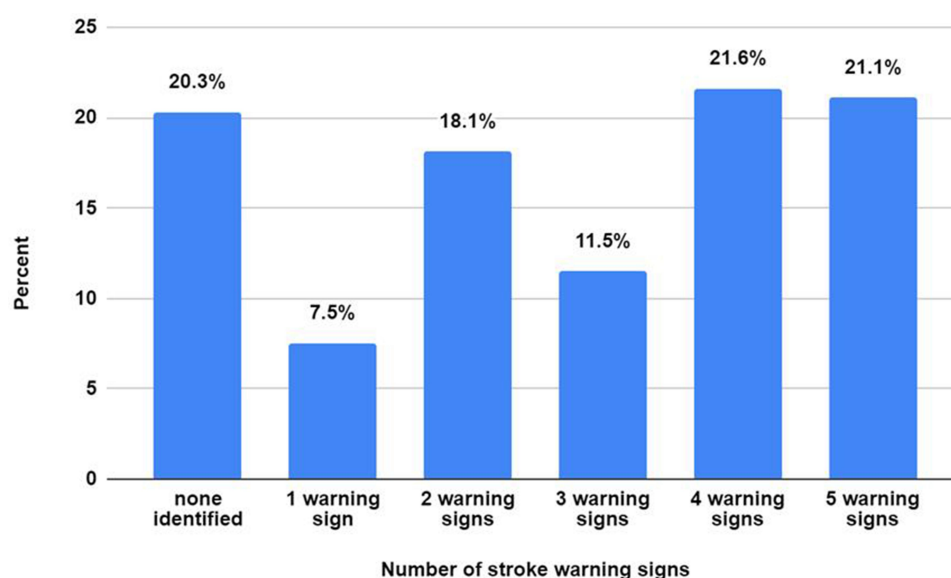
**Figure 2** Number of warning signs of stroke identified by patients with heart disease who were on follow-up at TASH, 2020.

Table 4 Binary Logistic Regression of Factors Associated with Knowledge of Stroke Risk Factors and Warning Signs Among Cardiac Patients Who Were on Follow-Up at TASH, 2020

Variables		Knowledge of Risk Factors		Knowledge of Warning Signs	
		P-value	OR (95% C.I)	P-value	OR (95% C.I)
Age	≥45 <45	0.050	2.03(1.00–4.12) I	0.202	1.69 (0.76–3.78)
Sex	Male Female	0.887	0.95 (0.46–1.95) I	0.458	0.74 (0.33–1.64) I
Marital status	Single Married Divorced Widowed	0.059 0.745 0.513 0.189	1.32 (0.25–7.02) 0.54 (0.09–3.40) 3.78 (0.52–27.56) I	0.265 0.982 0.901 0.196	1.02 (0.16–6.34) 1.14 (0.15–8.66) 4.12 (0.48–35.13) I
Occupation	Merchant Farmer Government employee House wife	0.154 0.248 0.055 0.013	2.19 (0.58–8.22) 10.74) 5.23 (1.41–19.39) I	0.158 0.100 0.141 0.032 0.606	3.40 (0.79–14.58) 2.81 (0.71–11.15) 5.17 (1.16–23.15) 1.36 (0.43–4.33)
Educational status	Secondary school or above Elementary school or less	0.030	2.28 (1.08–4.82) I	0.010	3.04 (1.31–7.08) I
Residence area	Urban Rural	0.076	2.18 (0.92–5.19) I	0.372	1.53 (0.60–3.90) I
Monthly income	≥5000 ETB <5000 ETB	0.437	1.40 (0.60–3.24) I	0.581	1.30 (0.51–3.32) I
Heard about a stroke before	Yes No	0.037	1.07 (0.50–2.23) I	0.024	1.49 (0.65–3.37) I
Know somebody with stroke	Yes No	0.010	2.83 (1.28–6.20) I	0.000	11.02 (4.42–27.46)

having a secondary/higher level of education were the predictors of good knowledge of risk factors (OR 3.19, 95% CI 1.70–5.74; $p = 0.003$) and (AOR=7.128, CI 95% 2.298–22.108) respectively.^{13,32} This similarity might be due to more literate can look up about their health from different sources. Contrasted to this study conducted in Turkey shows that there is no relationship between stroke knowledge and educational level.²⁹ The possible justification for this inconsistency was due to the study participant's difference among the studies.

Our study shows that age of patients, marital status, and sex of participants had no significant association (p -value >0.05) with knowledge of stroke risk factors and warning signs which is a contrast to studies conducted in Ethiopia that shows respondents aged <45 are more likely to have good knowledge of stroke risk factors and warning signs (AOR=2.56, CI 95% 1.115–6.015) than respondents who aged 45 years.¹³ This

study also contrasts with a study conducted in Korea that reveals a significant association between gender and age knowledge of stroke with good knowledge of stroke risk factors.³³ The possible reason might be due to socio-demographic differences among regions. However, our study findings were similar to studies conducted in Turkey which show there is no relationship of stroke knowledge with age ($p > 0.05$ each).²⁹ Furthermore, a study conducted in Nigeria shows sex and marital statuses of study participants were not predictors of knowledge of stroke risk factors and warning signs.²⁷

Limitation and Strength of the Study

The strength of this study was its attempts to generalize knowledge of stroke risk factors and warning signs with an appropriate selection of study area in which different

Table 5 Multivariate Logistic Regression of Factors Associated with Knowledge of Stroke Risk Factors and Warning Signs Among Cardiac Patients Who Were on Follow-Up at TASH, 2020

Variables		Knowledge of Risk Factors			Knowledge of Warning Signs		
		AOR (95% CI)	COR (95% CI)	P-value	AOR (95% CI)	COR 95% CI	P-value
Age	≥ 45 <45	1.8 (0.95–3.47)	1.63 (0.96–2.76) 1.00	0.069	1.66(0.81–3. 41)	1.55(0.91–2.64) 1.00	0.107
Sex	Male Female		0.86 (0.58–1.29) 1.00	0.898		0.82(0.48–1.40) 1.00	0.481
Marital status	Married Single Divorced Widowed		2.25 (0.57–8.83) 1.92(0.446–8.25) 5.87(1.07–32.02) 1.00	0.183		1.17(0.33–4.17) 1.52(0.39–5.97) 2.92(0.59–14.33) 1.00	0.349
Educational status	Elementary school or less Secondary school or above	1.00 3.05(1.62–5.74)	1.00 4.27(2.45–7.45)	0.005*	1.00 4.29(2.25–8.19)	1.00 4.91(2.7–8.68)	0.011*
Occupation	Farmer Merchant Govt. employee Housewife	1.00 2.61(0.93–7.30) 4.28 (1.32–13.89) 2.08(0.60–7.25)	1.00 4.36(1.58–12.04) 8.33(2.76–25.16) 1.07(0.41–2.81)	0.000	1.00 3.07(0.97–9.68) 3.78(1.10–12.97) 1.80(0.58–5.56)	1.00 3.77(1.39–10.21) 6.13(2.11–17.82) 0.84(0.323–2.19)	0.0001
Residence area	Urban Rural	2.07(1.05–4.1) 1.00	3.18(1.74–5.82) 1.00	0.036*		2.41(1.33–4.38) 1.00	0.004
Hearing about stroke	Yes No	2.67(1.24–5.76)	2.74(1.59–4.69) 1.00	0.000	1.73(0.80–3.78)	5.16(2.89–9.18) 1.00	0.017
Know somebody with stroke	Yes No	2.67(1.29–5.55)	2.82(1.43–5.54) 1.00	0.008*	11.11(5.24–23.59)	12.35(6.03–25.28) 1.00	0.000*

Note: *P-value <0.05 in multivariate logistic regression.

Abbreviations: AOR, adjusted odds ratio; COR, crude odds ratio.

regions of the country's patients were referred to it. Additionally, data quality control was highly practiced throughout the data collection as well as questionnaires were translated to two languages to interview participants.

Some limitations of the study were: firstly, since this study was limited by a single centered facility-based study selection bias can be an issue. Secondly, the study was limited to patients with heart disease only so it could not address the knowledge of stroke risk factors and warning signs in large populations in an ultimate way.

Conclusion

The study shows that participants had inadequate knowledge of stroke risk factors, with around one-fifth of the patients unable to identify any risk factors of stroke. More than half of patients had inadequate knowledge of warning signs of stroke and around one-fifth did not know any warning signs of a stroke. Educational status, residence area, and knowing somebody with stroke had a statistically significant association (p value<0.05) with adequate knowledge of stroke risk factors

and warning signs, while gender, sex, and marital status did not have a significant association with knowledge of risk factor and warning signs of a stroke.

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Disclosure

We disclose that this manuscript was based on Abdata Workina's Master's thesis. The authors report no conflicts of interest in this research work.

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