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Comparison of circulating lipid profiles, D-dimer and fibrinogen levels between hypertensive patients with and without stroke

Endeshaw Chekol Abebe [a,*], Misganaw Asmamaw Mengstie [a], Mohammed Abdu Seid [b], Natnael Atnafu Gebeyehu [c], Getachew Asmare Adella [d], Gizachew Ambaw Kassie [e], Molalegn Mesele Gesese [c], Kirubel Dagnaw Tegegne [f], Denekew Tenaw Anley [g], Sefineh Fenta Feleke [h], Melkamu Aderajew Zemene [g], Anteneh Mengist Dessie [g], Natnael Amare Tesfa [h], Natnael Moges [i], Ermias Sisay Chanie [i], Yenealem Solomon Kebede [j], Berihun Bantie [k], Tadesse Asmamaw Dejenie [l]

[a] Department of Biochemistry, College of Health Science, Debre Tabor University, Debre Tabor, Ethiopia
[b] Department of Physiology, College of Health Science, Debre Tabor University, Debre Tabor, Ethiopia
[c] Department of Midwifery, College of Medicine and Health Science, Wolaita Sodo University, Sodo, Ethiopia
[d] Department of Reproductive Health and Nutrition, School of Public Health, Woliata Sodo University, Sodo, Ethiopia
[e] Department of Epidemiology and Biostatistics, School of Public Health, Woliata Sodo University, Sodo, Ethiopia
[f] Department of Nursing, College of Medicine and Health Science, Wollo University, Dessie, Ethiopia
[g] Department of Public Health, College of Health Sciences, Debre Tabor University, Debre Tabor, Ethiopia
[h] School of Medicine, College of Health Sciences, Woldia University, Woldia, Ethiopia
[i] Department of Pediatrics and Child Health Nursing, College of Health Sciences, Debre Tabor University, Debre Tabor, Ethiopia
[j] Department of Medical Laboratory Science, College of Health Sciences, Debre Tabor University, Debre Tabor, Ethiopia
[k] Department of Comprehensive Nursing, College of Health Sciences, Debre Tabor University, Debre Tabor, Ethiopia
[l] Department of Medical Biochemistry, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia

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ABSTRACT

Background: Stroke is one of the leading causes of global mortality and disability, particularly in hypertensive patients. This study aimed to compare lipid profile, fibrinogen, and D-dimer levels between hypertensive patient with and without stroke.

Methods: This was a facility-based cross-sectional study conducted from November 2022 to January 2023 among 115 hypertensive patients (70 patients without stroke and 45 with stroke) who had follow-up at Yikatit 12 Hospital Medical College, Ethiopia. All data analyses were done using SPSS version 25.0 and comparisons of variables between groups were made using the Chi-square test, independent sample *t*-test, and Mann-Whitney *U* test. Multiple logistic regression analysis was done to identify predictors of stroke among hypertensive patients. A p-value <0.05 was assumed to be statistically significant for all statistical tests.

Results: Significantly elevated levels of TC, LDL-C, D-DI, and fibrinogen were observed in the stroke group than in the non-stroke group (p-value<0.05). The mean values of TC, D-DI, and fibrinogen were significantly higher in patients with ischemic stroke compared to those with hemorrhagic stroke. Duration of hypertension (AOR: 1.21; CI: 1.10, 2.09), TC (AOR:1.07; CI: 1.01, 1.22), D-DI (AOR: 1.15; CI: 1.05, 1.69) and fibrinogen (AOR:1.19; CI: 1.10, 2.89) were identified to be independent predictors of stroke in hypertensive patients.

Conclusion: The circulating levels of TC, LDL-C, D-DI and fibrinogen in hypertensive patients with stroke were significantly higher than in those without stroke. But only TC, D-DI, and fibrinogen were found to be predictors of stroke in hypertensives. Considerably higher TC, D-DI, and fibrinogen levels were also seen in patients with ischemic stroke than in those with hemorrhagic stroke. This confirms the key roles of dyslipidemia (hypercholesterolemia) and aberrant hemostatic activation to stroke development, notably ischemic stroke.

* Corresponding author. Department of Medical Biochemistry, College of Health Sciences, Debre Tabor University, Debre Tabor, Ethiopia; ;
E-mail address: endeshawchekole@gmail.com (E. Chekol Abebe).

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1. Introduction

Stroke is a sudden neurologic deficit that clinically manifests as cerebrovascular disease for at least 24 h [1]. More than 99% of strokes are due to arterial involvement, while less than 1% are due to venous involvement in the form of cerebral venous thrombosis. Among arterial causes, about 85% are due to infarction, known as ischemic stroke, and 15% are due to cerebral hemorrhage, called hemorrhagic stroke [2]. According to 2019 report, there were 12.2 million incident cases of stroke, 101 million prevalent cases of stroke, 143 million disability-adjusted life years (DALYs) due to stroke, and 6.55 million deaths from stroke. Globally, stroke is the second leading cause of death (11.6% of total deaths), and the third-leading cause of disability (5.7% of total DALYs) in 2019 [3]. In Ethiopia, stroke-related deaths account for 6.23% of all deaths, with an age-adjusted death rate of 89.82 per 100, 000 population [4]. There are numerous risk factors that have been linked to stroke development, such as diabetes, hypertension, dyslipidemia, cardiac disease, peripheral artery disease, and smoking [5]. It has been reported that 90% of the burden of stroke is attributable to modifiable risk factors [6].

Hypertension is the single most important modifiable cardiovascular risk factor that, in the long term, leads to complications such as stroke. It is linked to an increased risk of stroke and mortality [7–9]. Dyslipidemia, which is measured using serum lipid profile, is another modifiable risk factor that has been shown by some studies to be associated not only with the development of hypertension but also with stroke [10]. Many studies have identified elevated blood lipids as a risk factor for stroke or specific stroke types. An increased level of serum cholesterol (hypercholesterolemia) is a risk factor for both ischemic and hemorrhagic stroke [11]. On the contrary, other studies found that total cholesterol (TC) did not show an association with stroke [12,13]. With regard to stroke types, several clinical studies have reported a relationship between high levels of serum TC and ischemic stroke [12–14]. On the other hand, an indirect association has been shown between TC and hemorrhagic stroke [12–15]. In other studies, however, TC was not found to be associated with, or only had weak relationships with, different types of stroke [16,17]. The associations of other lipids, such as low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG), with stroke, especially type-specific stroke, were also discrepant [15,17,18].

Moreover, the activation of the hemostatic system has been identified as an important contributor to stroke. Hence, elevated thrombin generation and fibrin turnover, altered fibrinolytic activity, and disturbed endothelial function are commonly demonstrated in acute stroke [19,20]. Previous research has shown that D-DI and fibrinogen levels are important hemostatic factors linked to major cardiovascular events and stroke [21]. D-DI is a fibrin degradation product that is commonly considered a coagulation marker of thrombin generation and cross-linked fibrin turnover [22]. Several studies have indicated that high D-DI levels are strongly correlated to stroke diagnosis and incidence [23]. Presently, abnormally elevated D-DI level is a sensitive marker for thrombosis, which is clinically used to indicate pulmonary embolism (PE) or deep venous thrombosis (DVT) [24–27]. Many researchers have concluded that higher D-dimer levels are associated with a higher risk of stroke [28–30]. It has been shown that D-DI is associated with the neural damage biomarker in severe stroke, and it can predict stroke progression and death in acute stroke [31–34]. Nevertheless, a number of investigators did not reach conclusions on the relationship between D-DI and stroke [35,36].

Fibrinogen is a key coagulation factor that has a pivotal role in coagulation or thrombotic process. Plasma levels of fibrinogen could serve as independent predictors of vascular thrombosis involving the coronary, peripheral and cerebral arteries [37]. A number of studies have shown that fibrinogen is not only independently associated with the development of hypertension, but also with stroke [38,39]. Besides, while significant variations in fibrinogen levels have been observed between ischemic stroke and hemorrhagic stroke, other studies did not show any significant difference in fibrinogen levels between the two groups [40–43]. Despite the availability of data on the association of lipid profile, D-DI, and fibrinogen with stroke in various risk factors, the findings are controversial, and there is insufficient evidence evaluating the levels of these biomarkers in stroke patients coexisting with hypertension, particularly in Ethiopia. Hence, this study was aimed to compare lipid profile, D-DI, and fibrinogen levels between hypertensive patients with stroke and those without stroke. Besides, the levels of these biomarkers in ischemic and hemorrhagic stroke were compared in the study.

2. Method and materials

2.1. Study design, setting and population

In this facility-based cross-sectional study, a total of 115 hypertensive patients (70 patients without stroke and 45 patients with stroke) who came to a large urban teaching hospital, Yikatit 12 Hospital Medical College (Y12HMC) in Addis Ababa, Ethiopia, were recruited consecutively between November 2022 and January 2023. Known hypertensive patients with no evidence of stroke who attended the hospital for follow up were included in the study as non-stroke group. On the other hand, patients diagnosed with stroke (ischemic or hemorrhagic stroke) using brain CT-scan or MRI and within 24 h of admission to the emergency department were enrolled in this study as stoke group. But patients were excluded from the study if any of the following criteria were met: suspected DVT, PE, disseminated intravascular coagulation (DIC), recent surgery/trauma, pregnancy, age <18 years, diabetes mellitus, cardiac disease, or liver disease. No recruited patients received anticoagulatory (heparin or warfarin) or thrombolytic medication in the first 72 h of stroke onset.

2.2. Data collection procedures

Under close supervision, trained data collectors used a structured questionnaire to gather information from participants about their sociodemographic, behavioral, and clinical features through face-to-face interviews and chart reviews. In addition, anthropometric measurements like height and weight required to calculate BMI (kg/m2) were taken directly from each participant and recorded in the questionnaire. The weight of the participants was measured using a standard balance (in meters) while their height (in kilograms) was measured using a height measuring scale with light clothing and without shoes. After 15 min of rest, two consecutive measurements (taken on different occasions) of systolic blood pressure (BP) and diastolic BP were taken using a mercury sphygmomanometer, and the average of the two readings was used to determine the BP of each participant.

2.3. Blood sample collection and laboratory analysis

After informed consent, blood sample was taken from each participant within 24 h of admission but before treatment. For laboratory analysis of lipid profiles, the collected blood sample was added first into serum separator tubes (SST) and allowed to stand for 30 min at room temperature to clot. Then, the blood sample was centrifuged for 15 min at 3000 rpm to extract serum, and sent to the Ethiopian Public Health Institute (EPHI) to measure the levels of lipid profiles (TC, TG, HDL-C, and LDL-C). Serum lipid profiles were determined using a commercial kit developed by Cromatest® Cholesterol MR (Linear Chemicals S.L., Barcelona, Spain) was used. TC < 200; TG < 200; HDL>45; and LDL<100 were considered their respective normal reference ranges in mg/dl, whereas levels above/below these ranges were considered abnormal [44,45]. For the analysis of fibrinogen and D-DI, the drawn blood sample was poured into the EDTA-coated tube, and centrifugation was done within 4 h of blood collection. The plasma was then

transported to EPHI for analysis for D-DI and fibrinogen levels. While plasma D-DI was measured with the Tina-quant D-DI diagnostic test using a Roche COBAS 6000 auto-analyzer, plasma fibrinogen levels were measured by the Clauss clotting method [46]. Plasma D-DI levels range from 0 to 0.5 μg/mL, and fibrinogen levels range from 200 to 400 mg/dl were taken as normal [47].

2.4. Data processing and statistical analysis

After checking for completeness, the collected data were entered into SPSS version 25.0 for statistical analysis. While categorical variables were presented in frequency and percentage, continuous variables were expressed in mean and standard deviation (SD) (if normally distributed variables) and median and interquartile range (IQR) (if skewed variables). To determine the normality distribution of continuous data, the Kolmogorov–Smirnov test was used. A Chi-square test for categorical variables, an independent sample *t*-test for normally distributed continuous variables, and a Mann–Whitney *U* test for those skewed continuous variables were used to compare the differences of variables between the non-stroke and stroke groups as well as between patients with ischemic stroke and hemorrhagic stroke. The binary logistic regression model was employed to determine independent predictors of stroke among hypertensive patients. Variables with p-values <0.2 in bivariable logistic regression were exported into the multivariable logistic regression model for the final analysis. The Hosmer–Lemeshow test was employed to evaluate the fit and predictive accuracy of the final model. Adjusted Odds Ratio (AOR) at 95% CI was used to consider statistically significant predictors of the outcome variable. All statistical tests were two-tailed, and a p-value<0.05 was considered statistically significant.

3. Results

3.1. Socio demographic characteristics

A total of 115 (70 non-stroke and 45 stroke group) hypertensive patients were participated in this study. The mean (SD) age was significantly different between non-stroke group (47.7 ± 15.12 years) and stroke group (55.6 ± 15.71 years). But there were no observed significant variations between two groups on gender, marital status, education, occupation and residence. The details socio-demographic data of participants were shown in Table 1.

3.2. Behavioral and clinical characteristics

As shown in Table 2, approximately 5 (7.1%) and 4 (8.9%) participants in the non-stroke and stroke groups, respectively, had a smoking history. Thirteen (18.6%) non-stroke hypertensive patients and 11 (24.4%) stroke hypertensive patients had a history of alcohol consumption. The mean BMI of participants was 23.45 ± 4.98kg/m2 and 27.5 ± 4.52 kg/m2 in non-stroke and stroke groups, respectively. The mean systolic BP was 127.7 ± 21.69 mmHg for the non-stroke group and 132.7 ± 20.26 mmHg for the stroke group. On the other hand, the mean diastolic BP for non-stroke and stroke patients was 80.2 ± 10.61 mmHg and 82.9 ± 9.39 mmHg, respectively. The median duration of hypertension in those without stroke was 4 years (IQR = 4.25) and in those patients with stroke, it was 7.5 years (IQR = 6). While only 2 (2.9%) hypertensive patients currently without stroke reported a prior history of stroke, 3 (6.7%) hypertensive patients with current stroke did. Except for BMI, all these variables did not show any significant difference between the two groups (*P*-value >0.05).

3.3. Lipid profiles, D-DI, and fibrinogen in non-stroke and stroke groups

The findings of this study showed that the mean levels of circulating TG and D-DI were found to be higher than their respective cut-off values in the non-stroke group. However, with the exception of HDL-C, the mean values of circulating TC, TG, LDL-C, D-DI, and fibrinogen were above their normal ranges in hypertensive patients with stroke. Based on the results of an independent sample *t*-test, the mean levels of TC, LDL-C, D-DI, and fibrinogen were significantly higher (p-value<0.05) in the stroke group than in the non-stroke group. But there was no significant difference in serum TG and HDL-C between the two groups (Table 3).

Table 1
Socio-demographic characteristics of hypertensive patients with and without stroke.

Variables*	Category	Hypertensive patients (n = 115)		
		Non-stroke group (n = 70)	Stroke group (n = 45)	p-value
Age (year)	Mean ± SD	47.7 ± 15.12	55.6 ± 15.71	**0.021**
Gender	Male	29 (41.4%)	19 (42.2%)	0.812
	Female	41 (58.6%)	26 (57.8%)	
Marital status	Married	46 (65.7%)	31 (68.9%)	0.440
	Unmarried**	24 (34.3%)	14 (31.1%)	
Education	Illiterate	9 (12.9%)	9 (20.0%)	0.423
	Primary school	17 (24.3%)	10 (22.2%)	
	Secondary school	16 (22.9%)	15 (33.3%)	
	College/ university	28 (40.0%)	11 (24.4%)	
Occupation	Gov't employee	32 (45.7%)	16 (35.6%)	0.87
	House wife	19 (27.1%)	12 (26.7%)	
	Private employee	8 (11.4%)	7 (15.6%)	
	Merchant	6 (8.6%)	7 (15.6%)	
	Other***	5 (7.1%)	3 (6.7%)	
Residence	Urban	59 (84.3%)	37 (82.2%)	0.533
	Rural	11 (15.7%)	8 (17.8%)	

*Categorical data were expressed as frequency and percentages, n (%) and continuous variables presented as mean ± SD; **Single, divorced, and widowed; ***Car driver, student, daily laborer; *p-value written in **bold** indicates statistically significant (< 0.05).* ***Abbreviations:*** *SD, standard deviation.*

Table 2
Behavioral and clinical characteristics of non-stroke and stroke hypertensive patients.

Variables*	Category	Non-stroke group (n = 70)	Stroke group (n = 45)	*P*-value
Smoking status	Smoker	5 (7.1%)	4 (8.9%)	0.815
	None smoker	65 (92.9%)	41 (91.1%)	
Alcohol consumption	Yes	13 (18.6%)	11 (24.4%)	0.711
	No	57 (81.4%)	34 (75.6%)	
Physical activity	Yes	20 (28.6%)	9 (20.0%)	0.691
	No	50 (71.4%)	36 (80.0%)	
BMI (kg/m2)	Mean + SD	23.45 ± 4.98	27.5 ± 4.52	**0.013**
Systolic BP (mmHg)	Mean + SD	127.7 ± 21.69	132.7 ± 20.26	0.272
Diastolic BP (mmHg)	Mean + SD	80.2 ± 10.61	82.9 ± 9.39	0.438
Duration of hypertension (years)	Median (IQR)	4 (4.25)	7.5 (6)	0.172
Stroke type	Ischemic stroke	–	30 (66.7%)	–
	Hemorrhagic stroke	–	15 (33.3%)	
Previous stroke	Yes	2 (2.9%)	3 (6.7%)	0.723
	No	68 (97.1%)	42 (93.3%)	

Categorical data were expressed as frequency and percentages, n (%) and continuous variables presented as mean ± SD; p-value written in **bold** indicates statistically significant (< 0.05):* Abbreviations*: BMI, body mass index; BP, blood pressure; IQR, interquartile range; SD, standard Deviation.*

Table 3
Comparison of the mean levels of lipid profiles, D-DI, and fibrinogen in hypertensive patients without stroke and with stroke.

Variables	Mean ± SD		p-value*
	Non-stroke group (n = 70)	Stroke group (n = 45)	
TC, mg/dl	186.8 ± 37.2	239.1 ± 45.3	**0.019**
TG, mg/dl	202.1 ± 40.2	211.2 ± 34.9	0.509
HDL-C, mg/dl	62.2 ± 21.8	56.8 ± 29.3	0.612
LDL-C, mg/dl	92.1 ± 36.1	124.5 ± 23.8	**0.030**
D-DI, μg/ml	0.52 ± 0.14	0.74 ± 0.25	**0.002**
Fibrinogen, mg/dl	312 ± 70.2	405.9 ± 87.9	**0.001**

P-value < 0.05(written in **bold) considered statistically significant;* Normal ranges (in mg/dl): TC < 200; TG < 200; HDL>45; LDL<100; whereas for D-DI: 0–0.5 μg/mL, and fibrinogen: 200–400 mg/dl. ***Abbreviations:*** *D-DI, D-dimer; HDL-C, High density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SD, standard deviation; TC, total cholesterol; TG, triglyceride.*

3.4. Lipid profiles, D-DI, and fibrinogen in ischemic stroke and hemorrhagic stroke

In this study, the circulating levels of TC, TG, LDL-C, and D-DI were found to be above the normal ranges in both hypertensive patients with ischemic stroke and hemorrhagic stroke. The average fibrinogen levels were found to be elevated above the reference range in patients with ischemic stroke, but remained normal in patients with hemorrhagic stroke. The mean levels of serum HDL-C, on the other hand, remain within the normal ranges in both patients with ischemic stroke and hemorrhagic stroke. In comparison, the results from an independent sample *t*-test revealed significantly higher circulating mean values of TC, D-DI, and fibrinogen in patients with ischemic stroke than those with hemorrhagic stroke (Table 4).

3.5. Predictors of stroke among hypertensive patients

Of all demographic, behavioral, and clinical variables as well as biomarkers, only duration of hypertension (AOR: 1.21 for each year increase), TC (AOR: 1.07 for each mg/dl increase), D-DI (AOR: 1.15 for each unit increase), and fibrinogen (AOR:1.19 for each unit increase) were independent predictors of stroke in hypertensive patients (Table 5).

4. Discussion

Hypertension is one of the most important modifiable risk factors for stroke, and it has been linked to an increase in stroke incidence and mortality. This cross-sectional study was therefore aimed at comparing serum levels of lipid profile, plasma D-DI, and fibrinogen between hypertensive patients with stroke and those without stroke, as well as between the two stroke types. Based on the findings of the present study, the mean levels of circulating TC, TG, and LDL-C were above their normal ranges in hypertensive patients with stroke in contrast to non-stroke group. This confirms the results that high levels of serum TC and LDL-C have a strong association with the development of atherosclerosis, which leads to complications like stroke [48]. Denti et al. also reported partly consistent results with our study in that raised LDL-C levels and decreased HDL-C levels were associated with higher stroke risk [49]. This further corroborates that abnormal levels of the blood lipid profile are a risk factor for stroke and may play a considerable role in its development in hypertensive patients [50].

The current study also showed that the mean levels of TC and LDL-C were significantly higher in hypertensive patients who had stroke than in those who did not have stroke. Consistently, prior studies showed a statistically significant increase in levels of TC and LDL-C in patients with stroke in contrast to non-stroke control group [51–53]. This however conflicts with another study indicating no discernible difference in the TC levels between the two groups [50]. On the other hand, the levels of TG in our study were comparable between the two groups in contrast to a study by Li et al. [50]., which found that patients' serum TG levels were significantly higher in the stroke group than in the non-stroke group. In concordant with our results, several other studies also showed a statistically significant decrease in HDL-C in the stroke group when compared to non-stroke group [50,51,53] Furthermore, our study identified TC as an independent predictor of stroke in hypertensive patients, supporting that dyslipidemia, particularly hypercholesterolemia is an important risk factor linked stoke [18]. Conversely, stroke is reportedly associated with changes in the lipid levels, most likely as a result of the stress and excess catecholamine production that accompany acute stroke [52].

A number of previous studies have generally shown that patients with ischemic stroke had higher derangement of lipid profile than hemorrhagic stroke although the altered lipid profile varies in different studies [18,54]. In the present study, there was no significant difference in lipid profile among the ischemic and hemorrhagic stroke patients except for the TC values. Our results revealed a significantly higher values of serum TC in patients with ischemic stroke than in hemorrhagic stroke, which is line with other studies [17,54]. The finding was also supported by the results of many studies, showing a positive association between high levels of TC and ischemic stroke, indicating that an increased TC is strongly linked to a higher risk of developing ischemic stroke [12,14,18,55]. In contrary, an inverse relationship between TC and hemorrhagic stroke has been observed in other studies [56–58]. In several other reports, TC was not identified to be associated or showed only weak relationships with types of stroke [52,59–61].

On the other hand, our study demonstrated no significant difference between the ischemic and hemorrhagic stroke groups in the serum

Table 4
Comparison of the mean values of lipid profiles, D-DI, and fibrinogen between hypertensive patients with ischemic stroke and hemorrhagic stroke.

Variables	Mean + SD		p-value*
	Ischemic stroke (n = 30)	Hemorrhagic Stroke (n = 15)	
TC, mg/dl	244.1 ± 39.9	216 ± 42.2	**0.041**
TG, mg/dl	207.1 ± 44.7	216.2 ± 34.9	0.486
HDL-C, mg/dl	54.4 ± 27.6	59.1 ± 22.5	0.511
LDL-C, mg/dl	131.6 ± 21.9	115.7 ± 29.5	0.591
D-DI, μg/ml	0.79 ± 0.31	0.57 ± 0.22	**0.033**
Fibrinogen, mg/dl	427 ± 84.1	394 ± 79.7	**0.024**

P-value < 0.05(written in **bold) considered statistically significant;* Normal ranges (in mg/dl): TC < 200; TG < 200; HDL>45; LDL<100, whereas for D-DI: 0–0.5 μg/mL, and fibrinogen: 200–400 mg/dl.

Table 5
Multivariable binary logistic regression analysis to evaluate predictors of stroke among hypertensive patients.

Variables	AOR (95%CI)	p-value*
Age, years	1.18 (0.94, 1.33)	0.438
BMI, kg/m^2	0.91 (0.81, 3.02)	0.098
Systolic BP, mmHg	1.04 (0.99,1.08)	0.148
Diastolic BP, mmHg	0.95 (0.86, 2.04)	0.225
Duration of hypertension, years	1.22 (1.10, 2.09)	**0.029**
Prior stroke, yes	1.01 (0.83, 1.37)	0.891
TC, mg/dl	1.07 (1.01, 1.22)	**0.032**
TG, mg/dl	0.96 (0.98–3.02)	0.247
HDL-C, mg/dl	0.77 (0.96–2.98)	0.542
LDL-C, mg/dl	0.93 (0.95–1.31)	0.713
D-DI, μg/ml	1.15 (1.05, 1.69)	**0.022**
Fibrinogen, mg/dl	1.19 (1.03, 2.89)	**0.014**

*P-value<0.05(written in **bold**) considered statistically significant. **Abbreviations:** AOR, adjusted odds ratio; CI, confidence interval.

values of other lipid components (LDL-C, HDL-C, TG). This finding agrees with previous studies that found no statistical significance in the serum values of TG and LDL-C between ischemic and hemorrhagic stroke, although there were a significantly lower HDL-C levels in the former than the latter [54,61]. However, numerous studies have found significant variations in such lipid components with stroke type [58, 62–64].

Togha et al. showed a significantly elevated circulating levels of TG in patients with ischemic stroke than in those with hemorrhagic stroke [52]. Some studies demonstrated the positive association of elevated levels of TG, LDL-C and HDL-C with ischemic stroke, unlike hemorrhagic stroke [50,55]. When compared to hemorrhagic stroke, patients with ischemic stroke had higher LDL-C levels and lower HDL-C values [18]. This indicates that the relationships between lipid profiles and specific types of stroke are still a matter of controversy, that urges researchers to conduct further large-scale studies.

Moreover, the findings of our study indicated that D-DI and fibrinogen were reported to be elevated above their respective cut off values in patients with stroke. This supports the prior evidence of the link between coagulation activation and acute stroke [65–67]. The current study also revealed that the average levels of plasma D-DI in hypertensive patients with stroke were significantly higher than in the non-stroke group. This is congruent with another study that showed D-DI levels to be appreciably elevated in stroke patients compared to controls [68]. In addition, a plethora of other studies also reported similar findings, in which a significantly increased D-DI levels were noted in stroke patients compared to the apparently healthy controls [33,69,70]. Likewise, other researchers suggested that elevated levels of D-DI increase the risk of both ischemic and hemorrhagic stroke [25]. Further, we found that elevated levels of plasma D-DI were significantly associated with stroke after adjusting for confounders. This is supported by Smith et al. [71]., who reported that D-DI could predict incident stroke in the general population. Prior research also showed a significant association between a higher D-DI level and a greater risk of stroke [28–30,72]. In contrast, several prior studies did not arrive at conclusions on the relationship between stroke and D-DI [35,36].

Previous research has demonstrated that different forms of stroke are substantially associated with higher D-DI levels [69,73]. This coincides with our findings in which a significantly higher circulating mean values of D-DI were observed in patients with ischemic stroke than those with hemorrhagic stroke. It further bolstered the prior reports that D-DI levels are associated with the pathogenesis of ischemic stroke [32,74]. Besides, Folsom and collaborators found that higher plasma D-DI is a risk marker for ischemic stroke [75]. Nevertheless, the results of our investigation contradict those of a case-control study conducted by Kaplan et al. who revealed that D-DI was not an independent predictor of ischemic stroke [35]. In light of these findings, plasma D-DI levels might be helpful not only in diagnosis of stroke but also in differentiating ischemic stroke from hemorrhagic stroke in hypertensive patients.

Our study also showed statistically significantly elevated levels of fibrinogen in the stroke group in comparison to the non-stroke group. This is in line with other reports showing that serum fibrinogen levels were significantly higher in stroke patients than in controls [53,68,76]. Further analysis of our study also found that plasma fibrinogen were independent predictors of stroke in hypertensive patients. This was strengthened by previous studies in that elevated levels of fibrinogen have been reported after stroke and have been associated with an increased risk of recurrent stroke [41,77]. More intriguingly, we found a significantly increased circulating concentration of fibrinogen in ischemic stroke patients than those with hemorrhagic stroke. This is corroborated with the findings of other studies that indicated a significant variation of plasma fibrinogen between different types of stroke [68,72]. Another study also reported that patients with ischemic stroke had a significantly increased mean levels of fibrinogen, confirming that elevated plasma fibrinogen is a risk factor for ischemic stroke [37,40]. Our result, however, opposes the finding of a prior study that documented no significant difference in fibrinogen levels between patients with hemorrhagic stroke and ischemic stroke [40].

Collectively, the increased levels of fibrinogen in ischemic stroke may reflect an ongoing thrombus formation inside cerebral arteries Fibrinogen is a marker of thrombosis and inflammation, which can cause the migration and proliferation of smooth muscle cells, platelet aggregation, and vascular endothelial dysfunction. Hence, the increase in serum fibrinogen accelerates the formation of atheroma in the arteries and thus, indirectly involved in the development of ischemic stroke [40]. Besides, tis hemostatic marker is an acute-phase reactant that may participate in inflammation-mediated development of ischemic stroke. Therefore, it is possible that the raised fibrinogen levels in hypertensive patients can be utilized as markers for ischemic stroke and help to easily identify the type of stroke that occurred in those patients.

5. Limitation of the study

Although our study sheds light on comparison of lipid profile, D-DI, and fibrinogen in stroke and its types, it has some shortcomings. Firstly, blood samples were not taken immediately at the time of admission but instead were withdrawn as early as possible within 24 h of symptom onset. Secondly, this study did not consider factors such as age, obesity, and duration of hypertension that could change the level of D-dimer and fibrinogen and their short half-lives in thrombotic diseases. Thirdly, since the study employed a cross-sectional study design, it might not show the temporal relationship between cause and effect. The fourth one is that the study may have limited representativeness as it was conducted using small number of stroke patients.

6. Conclusion

In conclusion, our study demonstrated the presence of significantly elevated values of serum TC and LDL-C in hypertensive patients with stroke compared with those without stroke. However, only TC was found to be an independent predictor of stroke among hypertensive patients, supporting dyslipidemia, mainly hypercholesterolemia, as an essential risk factor for stoke. Ischemic stroke patients also had significantly higher serum TC levels than hemorrhagic stroke. Thus, serum TC could be used in the screening of high-risk patients for stroke as well as in differentiating ischemic stroke from hemorrhagic stroke. Besides, the variation of lipid levels in stroke types might have paramount importance for guiding lipid-lowering therapy, which can reduce the incidence and mortality of stroke by adapting primary and secondary preventive measures. But large-scale research is required to assess the impact of cholesterol lowering medication on morbidity and mortality in stroke patients.

The authors also confirmed that the levels of these hemostatic biomarkers were considerably higher in the stroke group than the non-stroke group and in ischemic stroke patients than hemorrhagic stroke patients. D-DI and fibrinogen were also predictors of stroke among patients with hypertension after controlling covariates. High levels of plasma D-DI and fibrinogen may indicate an increased risk stroke, particularly ischemic stroke. D-DI and fibrinogen may be used clinically in the future to screen patients at risk of stroke or clinically diagnose stroke. They may also shed light on potential stroke prevention strategies in the future, and it may be beneficial to research the advantages of lowering D-DI and fibrinogen levels in high-risk groups.

Ethical approval and consent to participate

All the experiments in this study were conducted in accordance to the Declaration of Helsinki. An ethical approval letter was obtained from the Department of Ethics and Research Committee (DRERC), Department of Medical Biochemistry, College of Health Sciences Debre Tabor University (DTU) and a written collaboration letter from Y12HMC was taken to carry out this study. The study objective was explained, and

written consent was obtained from each selected study participant. Participants were also informed that their participation is voluntary, that they can withdraw from the study at any time, and that their decision to continue or not in the study will not influence their provision of healthcare services. Confidentiality of information provided by participants was also kept by making the data collection procedure anonymous.

Authors contribution

ECA conceptualized the study: ECA, MAM, and TAD contributed during data collection, processing and analysis: NAG, MAS and GAA wrote the result interpretation: ECA, GAK, and MMG Prepared the first draft, KDT DTA, and SFF contributed during the conceptualization and interpretation of results and substantial revision: ECA, MAZ, NM, YSK, AMD, TDA, BB, SSF, GAK, MAM, AMD, MMG, DTA, KDT and GAA revised and finalized the final draft manuscript. All the authors read and approved the final version of the manuscript.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during this study are available from the corresponding author upon request.

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Declaration of competing interest

The authors declare that they have no competing interests.

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Lists of abbreviations

AAU	Addis Ababa University
AOR	adjusted odds ratio
BMI	body mass index
BP	blood pressure
CI	confidence interval
DALYs	Disability-Adjusted Life Years
D-DI	D-dimer
DIC	Disseminated Intravascular Coagulation
DRERC	Department of Ethics and Research Committee
DVT	Deep Venous Thrombosis
EPHI	Ethiopian Public Health Institute
HDL-C	High density lipoprotein cholesterol
ICH	intracerebral hemorrhage
IQR	interquartile range
LDL-C	low density lipoprotein cholesterol
PE	pulmonary embolism
SD	standard Deviation
SPSS	Statistical Package for Social Sciences
TC	total cholesterol
TG	triglyceride
Y12HMC	Yikatit 12 Hospital Medical College

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