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Research article

Diagnostic performance of plasma D-dimer, fibrinogen, and D-dimer to fibrinogen ratio as potential biomarkers to predict hypertension-associated acute ischemic stroke

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ABSTRACT

Background: Ischemic stroke is a common type of stroke that leads to death and functional disability in hypertensive patients. However, there are no well-studied non-invasive and less expensive fluid biomarkers routinely used to detect ischemic stroke in hypertensive patients. Hence, this study aimed to tease out the performance of D-dimer, fibrinogen, and the D-dimer to fibrinogen ratio (DDFR) in predicting hypertension-associated acute ischemic stroke.

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Methods: A hospital-based cross-sectional study was done from October 2022 to January 2022 at Yikatit 12 Hospital Medical College, Ethiopia. We recruited 55 hypertensive patients who had an ischemic stroke and 110 who did not. A ROC curve was used to calculate the areas under the curves (AUCs) and determine the diagnostic power of the D-dimer, fibrinogen, and DDFR. The Youden index was used to find the best cut-off points for biomarkers in detecting acute ischemic stroke. A De Long test was employed to show whether there was a significant difference between the AUCs of biomarkers in diagnosing ischemic stroke.
Results: D-dimer yielded the highest diagnostic power (AUC = 0.776) in detecting acute ischemic stroke, followed by DDFR (AUC = 0.763) and fibrinogen (AUC = 0.694), but there was no significant difference between them. At 0.52 μg/ml cut-off point, D-dimer had 82.9% sensitivity, 66.7% specificity, 62.5% PPV, and 85.3% NPV to diagnose acute ischemic stroke. Fibrinogen could detect acute ischemic stroke at 405.85 mg/dl level, with 70.0% sensitivity, 57.1% specificity, 41.2% PPV and 81.6% NPV. At a 1.83 ratio, DDFR might also identify ischemic stroke with 80.0% sensitivity, 67.1% specificity, 51.1% PPV, and 88.7% NPV.
Conclusion: We showed D-dimer, fibrinogen, and DDFR as promising, affordable, and non-invasive biomarkers for the detection of ischemic stroke among subjects with hypertension. This will help clinicians make an early diagnosis and better guide patient therapy.

1. Introduction

Ischemic stroke is a common type of cerebrovascular accident caused by the interruption of cerebral blood flow [1]. The 2019 global report showed that ischemic stroke represents more than 62% (7.6 million people) of all incident strokes, with a total of 3.3 million people worldwide dying from ischemic stroke. Over 63 million years of healthy life are lost each year globally due to ischemic stroke-related death and disability [2]. In Ethiopia, this type of stroke has also become the reason for 7.5–19.3% of hospital admissions and 6.23% of total deaths [3,4]. Ischemic stroke is becoming more common, endangering people's lives and quality of life. Patients with hypertension experience a considerably higher incidence of ischemic stroke, possibly by causing intracerebral vascular changes that enhance abnormal blood coagulation and by inducing inflammation [5–7].

Early detection and timely intervention of ischemic stroke are the best means to improve outcomes and reduce the disability of patients. Thus, it is worthwhile to detect ischemic stroke and manage it at the earliest possible stage [8]. Presently, the diagnostic and prognostic assessments of ischemic stroke widely use computed tomography (CT) scans and magnetic resonance imaging (MRI). Although these brain imaging methods are the gold standard, they are costly, time-consuming, and labor-intensive methods [9]. Hence, looking for simple, non-invasive, and less expensive circulating biomarkers is of great help in the early and accurate detection of acute ischemic stroke, especially in low-income countries [10].

D-dimer is a fibrin degradation product that plays a key role in the coagulation and fibrinolysis systems. Elevated D-dimer levels reflect an increase in blood coagulation, thrombin formation, and turnover of cross-linked intravascular fibrin [11]. Increased D-dimer concentration is also correlated with the increased risk of deep venous thrombosis (DVT), myocardial infarction (MI), pulmonary embolism (PE), surgery, disseminated intravascular coagulation (DIC), and trauma [12,13]. D-dimer is currently regarded as a non-invasive and highly sensitive biomarker of thromboembolic disorders like DVT and PE. Several studies have also shown that D-dimer is associated with a higher risk of stroke, mainly with acute ischemic stroke [14,15]. It has been shown that D-dimer plays a crucial role in stroke diagnosis, progression, and death [16–18]. The results of some prior studies demonstrated a positive correlation between elevated D-dimer levels and the occurrence of ischemic stroke [19–21]. Another study by Chen and colleagues also showed the potential role of D-dimer in detecting ischemic stroke [22]. Tzoulaki et al. on the other hand, discovered that D-dimer's predictive power was modest and its clinical relevance was unknown [23].

Fibrinogen is a liver-derived clotting factor involved in the regulation of primary homeostasis and platelet aggregation [24]. Elevated levels of plasma fibrinogen are associated with thrombotic processes and atherosclerosis involving the coronary, carotid, and peripheral arteries [25–27]. It is independently associated with the development of coronary artery disease, hypertension, and stroke [28–30]. Several reports have also indicated a significant relationship between elevated fibrinogen levels and the presence of ischemic lesions, likely as a result of the underlying inflammatory process [8,22,31]. It has been shown that circulating levels of fibrinogen are considerably raised in individuals with ischemic stroke [8,26,32]. Numerous epidemiological studies reported the role of fibrinogen as an acute-phase protein in inflammatory processes in cerebrovascular illness [33–36]. A few reports also indicated that high levels of fibrinogen may serve as a diagnostic predictor for the occurrence of acute ischemic stroke [8,31,37]. Although plasma fibrinogen serves as a predictor of vascular disease involving the coronary and peripheral arteries, in the case of cerebrovascular diseases like ischemic stroke, despite the positive results, the data is ambiguous and not adequately dependable [6,33].

Recently, the D-dimer to fibrinogen ratio (DDFR) has also been reported to be used to define the degree of thrombus activity in various thromboembolic diseases [24]. It is found to be an independent and novel predictor of different diseases, including PE, stroke, cardiovascular disease, and gastrointestinal stromal tumors (GIST) [38–41]. In emergency patients with no other medical condition, DDFR could be a specific diagnostic marker of PE [42]. Similarly, DDFR appears to be almost as useful in diagnosing PE as D-dimer [43]. Moreover, DDFR has been observed to be considerably higher in DVT patients than in non-DVT patients [44]. It has also been revealed that DDFR can be used as an effective biomarker for monitoring the prognosis of GIST patients [39]. Additionally, some studies have demonstrated a link between rising DDFR and stroke, particularly ischemic stroke [40]. It is also reported biomarker for

the diagnosis and prognosis of stroke, including ischemic stroke [40,41]. Although studies showing the relationship of D-dimer, fibrinogen, and DDFR with stroke were available, data reporting their performance in detecting ischemic stroke in patients with hypertension are limited. This study, therefore, aimed to evaluate the diagnostic performance of D-dimer, fibrinogen, and DDFR in detecting hypertension-associated ischemic stroke.

2. Methods

2.1. Study design, setting, and period

We conducted a hospital-based cross-sectional study for 3 months (from October 2022 to January 2022) at Yikatit 12 Hospital Medical College (Y12HMC) in Addis Ababa, Ethiopia.

2.2. Sample size determination and participants

Sample size (n) was calculated to be 165 using EPI info software version 7.2 by considering the expected proportion of outcome in the case group (P1) = 8.9%; the expected proportion of outcome in the control group (P2) = 0.09%; odds ratio (OR) = 18; ratio of control to the case (r) = 2, Z power = 80% and Zα/2 = 95%. Therefore, a total of 165 eligible hypertensive patients who had follow-ups at Y12HMC during the study period were recruited and classified into two groups. The first group included a total of 55 hypertensive patients with ischemic stroke diagnosed clinically and radiologically by either CT or MRI as a case group. In the case group, patients were recruited consecutively within 6 h of hospital admission to the emergency department. The second group involved 110 hypertensive patients without an ischemic stroke as a control group. The following exclusion criteria were applied to both groups during selection. We excluded patients with suspected DVT, PE, DIC, recent surgery/trauma (in the last 3 months), pregnancy, early age (<20 years), advanced age (>80 years), diabetes mellitus, renal failure, or liver disease, patients who were on anticoagulants before admission (heparin or warfarin), or oral contraceptives. Patients delayed more than 6 h after admission as well as patients with malignancy, febrile disorders, and inflammatory disease were also excluded.

2.3. Data collection and measurement

After informed consent was obtained from each study participant, all necessary information regarding sociodemographic and clinical characteristics was collected using a structured questionnaire by trained data collectors through face-to-face interviews and by reviewing the patient's medical records. Physical measurements like height and weight that are needed to calculate body mass index (BMI) were taken directly from each participant. Height was measured using a height measuring scale with light clothing and without shoes, and weight was measured using a standard balance. Blood pressure was measured using a mercury sphygmomanometer, and the average of two measurements was used to determine systolic blood pressure (SBP) and diastolic blood pressure (DBP) in each participant. A blood sample was drawn from each participant by qualified health professionals within 6 h of admission and poured into the EDTA tube. Next, centrifugation was carried out at 3000 rpm for 15 min at room temperature to obtain plasma. Plasma was then sent to the Ethiopian Public Health Institute (EPHI) for laboratory analysis in a cold box. Plasma D-dimer concentration (with the Tina-quant D-dimer diagnostic kit) and fibrinogen levels (the Clauss clotting method) were measured by using Roche COBAS 6000 and STA Compact auto-analyzer, respectively [45,46]. The DDFR was calculated using the equation: DDFR = D-dimer (μg/ml)/fibrinogen (mg/dl)*100[43].

2.4. Statistical data analysis

All statistical data analyses were made using SPSS version 25.0 and Med-Calc Statistical Software version 20.118. Categorical data were presented in frequency and percentage. After all data of quantitative variables were checked for normality using the Kolmogorov–Smirnov test, normally distributed variables were displayed as mean ± standard deviation (SD), and non-normally distributed (skewed) continuous variables were expressed as the median and interquartile range (IQR). The Chi-square test, independent sample *t*-test, or Mann–Whitney *U* test was used for the comparison of variables between hypertensive patients with ischemic stroke and those without. An adjusted logistic regression model was employed to determine the independent predictors of ischemic stroke in hypertensive patients by controlling potential confounders. The receiver operating characteristic (ROC) curve was constructed based on the best tradeoff between sensitivity and specificity to assess the diagnostic yield of D-dimer, fibrinogen, and their ratio (DDFR) in predicting ischemic stroke. The optimal cutoff points of these indicators were obtained based on the maximum Youden index (J) = maximum (sensitivity + specificity-1). The point corresponding to the maximum Youden's index was considered a cutoff value. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for stroke diagnosis were also measured. The areas under the ROC curves (AUCs) were calculated to figure out the diagnostic ability of these biomarkers in detecting ischemic stroke among hypertensive patients. A DeLong test was also performed to see the difference between these indicators in their predictive performance (AUCs). All statistical tests were two-tailed, and a p-value <0.05 at a 95% confidence interval (CI) was taken as statistically significant.

3. Results

3.1. Socio-demographic and clinical characteristics

This study included a total of 165 hypertensive patients (110 without stroke and 55 with ischemic stroke). The mean age of all patients was 48.7 ± 15.88, about 48% of them were male, and nearly 28% had a family history of hypertension. In all patients, the mean BMI was 25.3± 5.04, while the median duration of hypertension was five years (IQR = 6.5). Statistical tests revealed significant differences (p-value <0.05) in mean body weight, BMI, duration of hypertension, and SBP between those without stroke and those with ischemic stroke. However, there were no significant differences observed (p > 0.05) in mean age, sex, family history of hypertension, height, or DBP between the two groups. The socio-demographic and clinical characteristics of the study participants are summarized in Table 1.

3.2. Plasma D-dimer, fibrinogen and DDFR

The mean values of D-dimer were found to be substantially different between patients without and with ischemic stroke using the independent sample *t*-test, accounting for 0.44 ± 0.16 μg/ml and 0.56 ± 0.35 μg/ml, respectively. In hypertensive patients with ischemic stroke, we found a significantly higher mean fibrinogen concentration (401.27 ± 89.18 mg/dl) than in control groups (312.93± 67.14 mg/dl). Similarly, the DDFR in hypertensive patients with ischemic stroke was significantly higher than in those without stroke, with mean values of 1.97 ± 0.57 and 1.72 ± 0.51, respectively (Table 2).

3.3. Independent predictors of ischemic stroke in hypertensive patients

After adjusting for all possible confounders using multivariable logistic regression analysis, duration of hypertension, D-dimer, fibrinogen, and DDFR were identified to be significantly associated with ischemic stroke in hypertensive patients. For a unit increase in the duration of hypertension, there were 1.31 times (AOR: 1.31, 95%CI: 1.08, 1.75) more likelihood of having an ischemic stroke. Increasing plasma D-DI levels by one unit were 1.2 times (AOR: 1.20, 95%CI: 1.12, 2.96) higher odds of developing an ischemic stroke. The odds of hypertensive patients having an ischemic stroke increased by 1.08 times (AOR: 1.08, 95%CI: 1.04, 3.05) for every unit rise in plasma fibrinogen level. A one-unit increase in DDFR, on the other hand, raised the risk of getting ischemic stroke by 1.11 times (AOR: 1.11, 95%CI: 1.07, 1.47) (Table 3).

3.4. Diagnostic performance of D-dimer, fibrinogen, and DDFR

The diagnostic performances of these biomarkers in differentiating hypertensive patients with ischemic stroke from those without ischemic stroke were investigated using ROC curves. As depicted in Fig. 1 and Table 4, plasma D-dimer yielded the highest discriminative value with an area under the ROC curve (AUC) of 0.776 (95% CI:0.665–0.888), followed by DDFR, and fibrinogen with the overall diagnostic performance of 0.763 (95% CI:0.665–0.862) and 0.694 (95% CI:0.580–0.807), respectively.

3.5. Comparison of the diagnostic power of D-dimer, fibrinogen, and DDFR

Furthermore, our study compared the predictive models (AUC) of D-dimer, fibrinogen, and DDFR using the De Long test. Accordingly, the present study showed that there were no statistically significant differences (p-value>0.05) observed between these biomarkers in detecting hypertension-associated ischemic stroke (Table 5).

Table 1
Socio-demographic and clinical profiles of patients with and without ischemic stroke.

Variables	**All patients (n = 165)**	**Without ischemic stroke (n = 110)**	**With ischemic stroke (n = 55)**	p-value[a]
Age (year), mean ± SD	48.7 ± 15.88	46.0 ± 15.12	49.1 ± 15.88	0.855
Sex (male), n (%)	79 (47.9)	56(50.9)	22(40.0)	0.537
Family history of hypertension (yes), n (%)	46 (27.9)	27(24.5)	20(36.4)	0.475
Weight, mean ± SD	66.1 ± 13.33	64.0 ± 13.48	71.2 ± 11.72	0.038
Height, mean ± SD	1.62 + 0.09	1.62 ± 0.09	1.61 ± 0.08	0.608
BMI, mean ± SD	25.3 ± 5.04	24.4 ± 4.98	27.5 ± 4.52	0.042
Duration of hypertension (year), median (IQR)	5 (6.5)	4 [5]	8 [7]	0.027
SBP (mmHg), mean ± SD	129.2 ± 21.29	127.7 ± 21.7	139.7 ± 20.29	0.025
DBP (mmHg), mean ± SD	80.7 ± 10.24	80.2 ± 10.61	81.9 ± 9.40	0.459

[a] *Comparisons were made using independent sample t-test, Mann-Whitney test, or Chi-square test as appropriate. P-value <0.05 was considered statistically significant.* ***Abbreviations****: BMI, body mass index; DBP, diastolic blood pressure; IQR, interquartile range; SBP, systolic blood pressure; SD, standard deviation; n (%), frequency (percentage).*

Table 2
Mean levels of D-dimer, fibrinogen, and DDFR in patients with and without ischemic stroke.

Variables	Hypertensive patients(n = 165)		
	Without ischemic stroke (n = 110)	With ischemic stroke (n = 55)	p-value*
D-dimer (μg/ml), mean ± SD	0.44 ± 0.16	0.56 ± 0.35	<0.001
Fibrinogen (mg/dl), mean ± SD	312.93 ± 67.14	401.27 ± 89.18	0.001
DDFR, mean ± SD	1.72 ± 0.51	1.97 ± 0.57	<0.001

*p-value <0.05 was considered statistically significant. **Abbreviations:** DDFR, D-dimer to fibrinogen ratio.

Table 3
Independent factors for predicting ischemic stroke in hypertensive patients.

Variables	AOR	95% CI for AOR		*P*-value*
		Lower	Upper	
Age (years)	0.98	0.94	1.09	0.721
Weight (kg)	1.18	0.89	2.77	0.420
BMI (kg/m2)	1.44	0.74	1.89	0.093
Duration of hypertension (years)	1.31	1.08	1.75	0.034
SBP (mmHg)	1.03	0.98	1.09	0.172
DBP (mmHg)	0.94	0.85	1.042	0.248
D-dimer (μg/ml)	1.20	1.12	2.96	0.003
Fibrinogen (mg/dl)	1.08	1.04	3.05	0.029
DDFR	1.11	1.07	1.47	0.011

*p-value <0.05 considered statistically significant. **Abbreviations**: AOR, adjusted odds ratio; *BMI, body mass index;* CI, confidence interval; *DBP, diastolic blood pressure;* DDFR, D-dimer to fibrinogen ratio; *SBP, systolic blood pressure*.

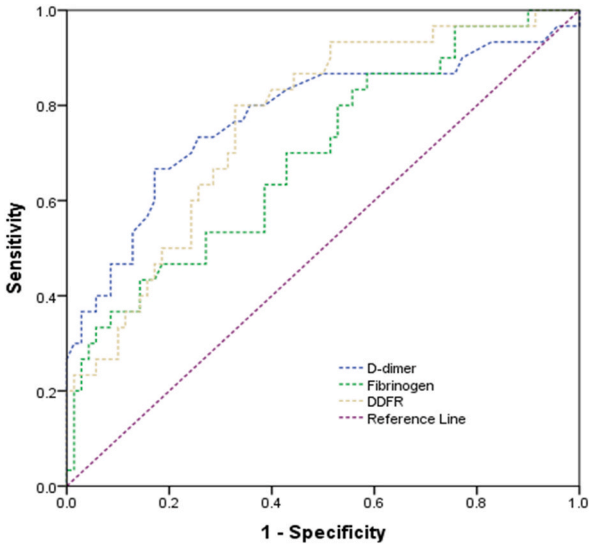

Fig. 1. ROC curve analysis of D-dimer, fibrinogen, and DDFR in predicting acute ischemic stroke in hypertensive patients.

Table 4
The AUC of biomarkers for diagnosing hypertension-associated ischemic stroke.

Variables	AUC	SE	p-value	95%CI	
				Lower bound	Upper bound
D-dimer	0.776	0.057	0.001	0.665	0.888
Fibrinogen	0.694	0.058	0.002	0.580	0.807
DDFR	0.763	0.050	0.001	0.665	0.862

Abbreviations: AUC, area under the ROC curve; CI-Confidence interval; SE, Standard error.

Table 5
Comparison of AUC of diagnostic tests to predict ischemic stroke using DeLong test.

Contrast	Difference	SE	p-value	95%CI	
				Lower bound	Upper bound
D-dimer – DDFR	0.053	0.0571	0.811	−0.099	0.125
Fibrinogen - DDFR	0.029	0.0757	0.721	−0.077	0.220
D-dimer- Fibrinogen	0.085	0.0504	0.605	−0.014	0.183

3.6. Cut-off value, sensitivity, specificity, PPV, and NPV of biomarkers

Using ROC curve analysis, the Youden index (J) was determined and used to establish the appropriate cut-off value for these biomarkers as diagnostic tests for ischemic stroke in hypertensive patients. Based on this analysis, the optimal cut-off points were 0.52 μg/ml, 405.85 mg/dl, and 1.83 for D-dimer, fibrinogen, and DDFR, respectively. D-dimer had a sensitivity of 82.9%, a specificity of 66.7%, a PPV of 62.5%, an NPV of 85.3%, and an accuracy of 78.0% in differentiating ischemic stroke in hypertensive patients. Within the given cut-off point, plasma fibrinogen was found to have the ability to predict ischemic stroke among hypertensive patients with a diagnostic yield of 70.0% sensitivity, 57.1% specificity, 41.2% PPV, 81.6% NPV, and 61.0% accuracy. With the mentioned cut-off value, DDFR can discriminate hypertensive patients with ischemic stroke from those without stroke, with 80.0% sensitivity, 67.1% specificity, 51.1% PPV, 88.7% NPV, and an accuracy of 71.0% (Table 6).

4. Discussion

This study was primarily aimed at evaluating the diagnostic abilities of D-dimer, fibrinogen, and DDFR in detecting ischemic stroke in patients with hypertension. Our results demonstrated an independent association of D-dimer levels with ischemic stroke, which is in agreement with other pieces of literature [19–21]. D-dimer has long been used as a valuable marker of activation of fibrinolysis secondary to acute thrombosis, and hence, it has been thoroughly investigated for the diagnosis of venous thromboembolism (VTE) [47]. Nowadays, it is routinely employed in clinical practice as a non-invasive and highly sensitive biomarker of thromboembolic disorders involving DVT and PE [13,48]. D-dimer has also a role in determining the best anticoagulation duration for patients with VTE, for DIC diagnosing and monitoring, and as a tool for identifying individuals with high risk for VTE [49]. Some prior studies have also shown the use of D-dimer in stroke diagnosis, progression, and death [17,18,50,51]. We indicated that, with 77.6% of performance, D-dimer could identify ischemic stroke among hypertension patients. This finding coincides with Chen et al. who documented the role of D-dimer in detecting ischemic stroke [22]. Nonetheless, another prospective research found that the predictive ability of D-dimer was modest, and clinical utility was uncertain [23]. This warrants the need of more research with improved methodology before utilizing it at clinical settings as a diagnostic marker.

Besides, our study showed that the cut-off point of D-dimer for distinguishing hypertensive patients with ischemic stroke from those without stroke was 0.52 μg/ml, yielding a sensitivity of 82.9%, a specificity of 66.7%, a PPV of 62.5%, and NPV of 85.3%. This reveals that D-dimer has good sensitivity and NPV but poor specificity and PPV for detecting ischemic stroke. These features of D-dimer for the identification of ischemic stroke are consistent with its ability to diagnose DVT and PE, which have high sensitivity and NPV but low specificity and PPV for these disorders [48,52,53]. In other words, when it gets raised, D-dimer plays a crucial role as an exclusionary diagnostic test to rule in thrombotic disorder without further imaging. This highlights that D-dimer can be utilized as a low-cost and promising diagnostic marker to detect ischemic stroke associated with hypertension. This is especially very helpful in areas with low socio-economic status where imaging techniques like CT scan are not available and affordable. In addition, D-dimer can also be utilized as a screening marker for detecting ischemic stroke in patients with hypertension at the earliest possible stage before a full-blown stroke occurs.

Furthermore, the current study indicated that fibrinogen is an independent predictor of ischemic stroke and that its circulating level is considerably higher in people who have had an ischemic stroke, which is in line with previous findings [8,26,32]. A plethora of earlier studies have also revealed the positive relationship of fibrinogen levels with the acute phase of cerebral infarction [31,54–56]. The existence of an inflammatory process that underpins ischemic stroke and causes acute phase response proteins, including fibrinogen, to increase in the bloodstream is suggested as the possible cause of the elevated fibrinogen levels [22]. More intriguingly, our study discovered plasma fibrinogen may serve as a biomarker to detect ischemic stroke in individuals with hypertension, with about 69.4% diagnostic power. Accumulating evidence demonstrates that fibrinogen can be used as a biomarker of thrombosis and inflammation [33–36]. Samir and colleagues showed that high levels of fibrinogen could be used as a predictor for the occurrence of

Table 6
The clinical performance of biomarkers in diagnosing acute ischemic stroke among hypertensive patients.

Variables	Youden index (J)	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
D-dimer (μg/ml)	0.495	0.52	82.9	66.7	62.5	85.3	78.0
Fibrinogen (mg/dl)	0.471	405.85	70.0	57.1	41.2	81.6	61.0
DDFR	0.271	1.83	80.0	67.1	51.1	88.7	71.0

Abbreviations: PPV, Positive Predictive Value; NPV, Negative Predictive value.

acute ischemic stroke [31]. Congruently, Peycheva et al. found that fibrinogen levels had a statistically significant (albeit weaker) diagnostic performance in differentiating ischemic stroke [8]. Additionally, our finding was corroborated by the Copenhagen City Heart Study, indicating that fibrinogen is a predictive marker of ischemic stroke [37].

Besides, this study found that the optimum cut-off value of fibrinogen for distinguishing between the presence and absence of acute ischemic stroke in hypertensive patients was 405.85 mg/dl, which had diagnostic yields of 70.0% sensitivity, 57.1% specificity, 41.2% PPV, and 81.6% NPV. According to a prior study, plasma fibrinogen indicates the presence of ischemic lesions with a sensitivity of 59% and specificity of 69.6% at 341 mg/dl [8]. Other studies have also reported that fibrinogen can determine the onset of ischemic stroke with a cut-off value of 439 mg/dl [25,31,37,57] Altogether, fibrinogen can predict ischemic stroke among hypertensive patients although it has a lower diagnostic performance than D-dimer. It may be a less specific and, hence, less useful marker than D-dimer to be used as a reliable diagnostic test for ischemic stroke. This may be due to the erratic fluctuation of blood fibrinogen levels in patients with ischemic stroke. Fibrinogen can be consumed and reduced if there is blood coagulation, but it could increase when there is inflammation [22,43]. However, the authors suggest using fibrinogen as a biomarker for ischemic stroke by combining it with other hemostatic factors with caution. We also recommend further studies with a strong study design that will provide additional evidence to use fibrinogen clinically.

Moreover, this study showed DDFR as an independent predictor of ischemic stroke in hypertensive patients. We found that DDFR had good diagnostic efficacy in detecting acute ischemic stroke. The role of DDFR as a biomarker for a variety of diseases was reported in several prior studies. According to research by Kucher and colleagues, in emergency patients with no other medical condition, DDFR could be a specific predictor of PE [42]. Likewise, another report demonstrated that DDFR appears to be almost as helpful as D-dimer in identifying PE [43]. Besides, Wuillemin et al. reported that DDFR was significantly higher in DVT patients than in those who did not have DVT[44]. Another study also revealed that DDFR can be used as an effective biomarker for monitoring the prognosis of GIST patients [39]. Congruent with our findings, recent studies have also reported DDFR as a useful biomarker for the diagnosis and prognosis of stroke, especially ischemic stroke [40,41]. We observed that DDFR can discriminate hypertensive patients with ischemic stroke from those who do not, with an overall diagnostic power of 76.3%. Although not statistically significant, the diagnostic efficacy of DDFR was better than that of D-dimer but less than that of fibrinogen. On the contrary, Kara et al. found that DDFR has a two-fold better diagnostic performance compared to D-dimer in detecting PE [38]. On the other hand, Chen et al. reported that DDFR has equal diagnostic efficacy at detecting acute ischemic stroke as D-dimer [22].

Besides, the present study indicated that DDFR has 80.0% sensitivity, 67.1% specificity, 51.1% PPV, and 88.7% NPV at the optimal cut-off point of 1.83. This shows that DDFR is superior to fibrinogen in all parameters of the diagnostic test for identifying ischemic stroke in hypertensive patients. However, DDFR has a lower sensitivity and PPV than D-dimer, which is in line with another study [38]. It has also a better specificity and NPV than D-dimer to diagnose ischemic stroke. Our finding opposes another research that highlighted a comparable specificity between DDFR and D-dimer in screening ischemic stroke [22]. However, our results agree with other reports showing that the specificity of DDFR to detect thrombosis was greater than plasma D-dimer for the detection of PE, DVT, and ischemic stroke [38,40,44]. This suggests that, like D-dimer and fibrinogen, DDFR could serve as a valuable biomarker for diagnosing ischemic stroke, with greater specificity and NPV than D-dimer and fibrinogen.

Taken together, these hemostatic biomarkers may be valauble candidates as markers of acute ischemic stroke due to their good diagnostic performance and undeniably lower cost, invasiveness, and labor intensity than imaging techniques. Thus, such fluid markers may be helpful in the primary prevention, diagnosis, and treatment guidance of hypertensive patients with ischemic stroke. Despite the strengths of our study, there are some shortcomings. Firstly, this small sample size and single-center study may limit the generalizability of our findings to other settings. Secondly, since the study employed a cross-sectional study design, it may be difficult to differentiate the causes and effects. Besides, we only measured the admission D-dimer and fibrinogen levels, and the dynamic changes of the biomarkers were not analyzed.

5. Conclusion

To wrap up, the present study identified plasma D-dimer, fibrinogen, and DDFR as potentially useful biomarkers that can facilitate the clinical diagnosis of ischemic stroke in hypertensive patients. The diagnostic performance for ischemic stroke was highest for the D-dimer, followed by the DDFR and fibrinogen. While D-dimer had the highest sensitivity and PPV, DDFR was superior in specificity and NPV. Because these biomarkers are easily accessible, less invasive, and cost-effective tests, they can be used for the timely detection of acute ischemic stroke and early onset intervention aimed at modifying hemostatic activation. Besides, the biomarkers will be conducive to opening up a great deal of potential for expanded clinical access and more efficient population screening. Our work also provides a robust baseline for conducting further multicenter studies to verify and extend the present findings to other clinical situations. However, none of these hemostatic biomarkers could replace brain CT scans or MRIs in the definitive diagnosis of ischemic stroke in clinical settings.

Ethical approval and consideration

All the experiments in this study were conducted in accordance with the Declaration of Helsinki. An ethical approval letter 04/14 was obtained from College of Health Sciences in 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.

Consent for publication

Not applicable.

Disclosure of interest

The authors declare that they have no competing interests.

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Author contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, data acquisition, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing for important intellectual content. All authors read and gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Data availability statement

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

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

AOR	adjusted odds ratio
AUC	areas under the ROC curve
BMI	body mass index
CI	confidence interval
CT	computed tomography
CVD	Cardiovascular disease
DBP	diastolic blood pressure
DDFR	D-dimer to fibrinogen ratio
DIC	disseminated intravascular coagulation
DRERC	Department of Ethics and Research Committee
DVT	deep venous thrombosis
EPHI	Ethiopian Public Health Institute
GIST	gastrointestinal stromal tumor
IQR	interquartile range
MI	myocardial infarction
MRI	magnetic resonance imaging
NPV	Negative Predictive value
PE	pulmonary embolism
PPV	Positive Predictive Value
ROC,	receiver operating characteristic
SBP	systolic blood pressure
SD	standard deviation
VTE	venous thromboembolism

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27192.

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