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Prognostic Value of Delta Fibrinogen for tPA-Related Intracranial Hemorrhage: A Prospective Emergency Department Cohort Study

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Abstract

Background: Intravenous thrombolysis is a cornerstone therapy for acute ischemic stroke; however, treatment-related intracranial hemorrhage (ICH) remains a major clinical challenge. Identifying early, practical biomarkers that may help predict post-thrombolysis hemorrhagic complications is of significant importance. This study aimed to evaluate whether early fibrinogen variation within the first three hours after intravenous tissue plasminogen activator (IV tPA) administration is associated with 24-hour ICH.

Methods: This single-center prospective cohort study included adult patients treated with IV tPA between October 2023 and February 2025. Baseline fibrinogen and 3-hour post-treatment fibrinogen levels were obtained, and delta fibrinogen was calculated. Routine 24-hour cranial CT was used to detect ICH. Subtypes were classified as HI1, HI2, PH1, or PH2. ROC analysis was performed to assess diagnostic performance.

Results: A total of 105 patients were analyzed, of whom 21 (20%) developed ICH. Delta fibrinogen decline was significantly greater in the ICH group compared with the non-ICH group (200 mg/dL vs. 48.25 mg/dL; $p = 0.009$). Subgroup analysis showed that parenchymal hematoma (PH1/PH2) was strongly associated with greater fibrinogen reduction ($p = 0.03$). ROC analysis yielded an AUC of 0.748 for predicting PH, with an optimal cut-off of 158 mg/dL (sensitivity 74.7%, specificity 80.0%). Patients with PH had significantly worse 3-month functional outcomes and higher mortality ($p < 0.05$).

Conclusion: Early fibrinogen decline within the first three hours after IV tPA is significantly associated with 24-hour ICH, particularly parenchymal hematoma. Monitoring fibrinogen kinetics may enhance early risk stratification and support clinical decision-making in the post-thrombolysis period.

Introduction

Ischemic stroke (IS) is defined as the reduction of cerebral blood flow due to embolism, thrombosis, or systemic hypoperfusion [1]. It is a major cause of morbidity and mortality worldwide, with substantial global health and economic impacts. According to data from the United States of America (USA), approximately 795,000 individuals experience a stroke each year, and nearly 75% of these are classified as IS [2]. Timely reperfusion therapy is critical, and thrombolysis with intravenous tissue plasminogen activator (tPA) remains the standard treatment within the therapeutic window. Administration within the first 4.5 hours is strongly associated with improved functional outcomes [3]. One of the most severe and potentially fatal complications of tPA is intracranial hemorrhage (ICH). Symptomatic ICH occurs in approximately %1.8-5.0 of patients receiving thrombolytic therapy [4, 5].

Due to the high clinical significance of this complication, multiple clinical, radiological, and biochemical indicators have been evaluated as potential predictors of ICH in patients treated with tPA. Previous studies have identified several risk factors, such as advanced age, hyperglycemia, hypertension, large

infarct size, atrial fibrillation, and microbleeds detected on susceptibility-weighted imaging magnetic resonance imaging (SWI MRI), that may increase the likelihood of post-thrombolytic ICH [6].

Fibrinogen plays a crucial role in clot formation and has been shown to decrease following thrombolytic therapy due to enhanced plasmin activity [7]. However, limited evidence exists regarding the early post-thrombolysis kinetics of fibrinogen and its association with ICH. This lack of evidence underscores the need for prospective studies to determine whether early fibrinogen level variation can serve as a prognostic indicator for 24-hour ICH. The objective of this cohort study is to investigate the prognostic value of early fibrinogen level variation in predicting ICH in patients receiving IV tPA for acute ischemic stroke. We hypothesize that early variation in fibrinogen levels after IV tPA administration may serve as a predictive marker for intracranial hemorrhage

Methods

Study Design and Settings

This was a single-center, prospective, observational cohort study. The study was conducted between October 2023 and February 2025 at Marmara University Department of Emergency Medicine, a tertiary care facility and certified stroke center, which provides a 24-hour, 7-day-a-week stroke team, including an interventional radiologist. All participants or their legally authorized representatives provided written informed consent prior to inclusion in the study. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and STROBE guidelines [8].

Study participant

The study included adult patients (≥ 18 years) who presented with acute ischemic stroke and were within the therapeutic window for intravenous thrombolysis. Eligible participants were those within 4.5 hours of symptom onset, as well as patients with wake-up stroke who fulfilled the clinical and radiological criteria defined in current stroke management guidelines [9, 10].

Written informed consent was obtained from all participants. Patients were excluded if they were pregnant or had a known fibrinogen-related disorder, and participants were withdrawn if coagulation parameters could not be obtained (not drawn or results were coagulated), or if the primary outcome could not be achieved (transport to another facility, unavailable cranial CT, or withdrawn consent).

Study Procedure, Variables, and Definitions

In the presence of presenting symptoms such as altered mental status, dysarthria, or unilateral weakness, the institutional stroke code protocol was activated. The stroke team was then alerted, and the patient referred accordingly. Blood samples were drawn, including complete blood count, renal and liver function tests, high-sensitivity troponin-T, and coagulation parameters with fibrinogen. Patients were

subsequently sent for immediate cranial imaging. If the patient had an indication, intravenous thrombolytic therapy was initiated immediately, and a second venous blood sample was obtained 3 hours after treatment. The difference between the baseline and the 3-hour fibrinogen levels was described as delta-fibrinogen. A routine cranial CT scan was performed 24 hours after thrombolysis, in accordance with current guideline recommendations, to evaluate for ICH [9]. If the patient's neurological status deteriorated after tPA was administered, an urgent cranial CT also was performed immediately. Variables included patient age, admission vital signs, presenting Glasgow Coma Scale (GCS) score (19), and chronic comorbidities such as hypertension (HT), diabetes mellitus (DM), coronary artery disease (CAD), previous IS, congestive heart failure (CHF), and dysrhythmia. Presenting symptoms, such as limb weakness, dysarthria, and other focal neurological deficits, were recorded upon emergency department evaluation. The use of antiplatelet or anticoagulant medications before presentation also documented. The time from symptom onset to IV tPA was documented in minutes. Blood pressure values were recorded at 15-minute intervals during tPA administration, in accordance with standard monitoring protocols [9]. Neurological status was assessed using the National Institutes of Health Stroke Scale (NIHSS) at baseline and after the completion of tPA infusion [10]. Functional outcome was evaluated using the modified Rankin Scale (mRS) at both hospital discharge and 3-month follow-up, which was conducted via outpatient clinic visits or telephone interviews (20).

Outcomes

The primary outcome of the study was the presence of ICH detected on routine 24-hour CT following intravenous thrombolytic therapy. The secondary outcome was 3-month functional status, assessed using the mRS, obtained during outpatient follow-up or telephone interviews. Intracranial hemorrhage (ICH) detected on cranial CT performed within 24 hours was radiologically classified as hemorrhagic infarction type 1 (HI1), type 2 (HI2), parenchymal hematoma type 1 (PH1), or type 2 (PH2) based on previously established imaging criteria [12]. All CT scans were interpreted through consensus reading by a neurologist and an emergency medicine specialist. If there was any conflict in determining, the radiologist made the final decision.

Sample Size and Statistics

The sample size was calculated based on an estimated overall incidence of post-thrombolytic intracranial hemorrhage (including both HI and PH), reported as approximately 23.4% in prior studies [10]. The sample size was calculated using G*Power software [11]. Assuming a type I error of 5% ($\alpha = 0.05$) and a power of 80% ($1-\beta = 0.80$), the minimum required sample size was determined to be 80. All statistical analyses were performed using SPSS version 22.0 and the open-source R-based software Jamovi. Categorical variables were expressed as counts and percentages, while continuous variables were assessed for normality using the Shapiro–Wilk test or histogram. Normally distributed data were presented as mean ± standard deviation (SD), whereas non-normally distributed variables were reported as median and interquartile range (IQR). Comparisons between groups were made using the Student's t-

test or the Mann-Whitney U test for continuous variables and the Pearson chi-square or Fisher's exact test for categorical variables. Receiver operating characteristic (ROC) curve analysis was used to determine optimal cut-off values for fibrinogen levels (12). Multivariate regression analyses were conducted to identify independent predictors of intracranial hemorrhage. In all analyses, p-values of < 0.05 were considered statistically significant.

Results

Study Population

During the study period, 155 patients presented to Marmara University Department of Emergency Medicine with a diagnosis of acute IS. 25 patients were excluded due to absolute contraindications for IV tPA. Among the remaining 130 patients, three declined to provide informed consent for participation in the study. A total of 127 patients received IV tPA; however, 15 of these were excluded due to missing follow-up fibrinogen measurements. Two patients died within the first 24 hours before cranial CT imaging could be performed. Four patients were transferred to intensive care units at other healthcare facilities. 1 patient withdrew consent after enrollment. After excluding all patients who met the exclusion criteria, 105 patients were included in the final analysis (Fig. 1).

Baseline Characteristic

A total of 105 patients were included in the study, of whom 46 (43.8%) were female (mean age: 75.4 ± 11.4 years) and 59 (56.2%) were male (mean age: 66.8 ± 12.7 years). Of these, 21 patients (20%) developed ICH (ICH group) on follow-up cranial CT, and 84 patients (80%) did not develop ICH (non-ICH group). Subtypes of ICH included eight patients with HI1 (7.6%), three with HI2 (2.9%), three with PH1 (2.9%), and seven with PH2 (6.7%).

NIHSS scores at admission were significantly higher in the ICH group compared to the non-ICH group ($p = 0.002$; 95% CI: − 1.27 to − 0.283). GCS scores were significantly lower in the ICH group ($p < 0.001$; 95% CI: 0.169 to 1.146). Additionally, the proportion of patients receiving acetylsalicylic acid (ASA) prior to stroke was significantly higher in the ICH group than in the non-ICH group (42.9% vs. 25.0%, $p = 0.015$). No statistically significant differences were observed between the ICH and non-ICH groups in terms of chronic comorbidities such as hypertension, diabetes mellitus, coronary artery disease, dysrhythmia, or prior ischemic stroke (all analyses $p > 0.05$). Baseline demographic characteristics and laboratory findings of patients with and without ICH are presented in Table 1.

Table 1
Patients' baseline characteristics

Variables	All (n = 105)	Non-ICH group (n = 84)	ICH group (n = 21)	p value
Age, years mean ± SD	70.6 ± 12.8	70.5 ± 12.8	70.8 ± 13.1	0.943£
Male gender, n (%)	59 (56.2)	48 (57.1)	11 (52.4)	0.694^
Comorbidities, n (%)				
Hypertension	66 (62.9)	53 (63.1)	13 (61.9)	0.920^
Diabetes Mellitus	44 (41.9)	35 (41.7)	9 (42.9)	0.921^
CAD	30 (28.6)	21 (25)	9 (42.9)	0.105^
Previous IS	14 (13.3)	11 (13.1)	3 (14.3)	1.000*
Dysritmia	22 (20.9)	19 (22.6)	3 (14.3)	0.551*
CHF	11 (10.5)	8 (9.5)	3 (14.3)	0.690*
Vital Sign				
Systolic BP mean ± SD	154 ± 28.2	153 ± 28.4	157 ± 28	0.558£
Diastolic BP mean ± SD	88.2 ± 16.3	88.4 ± 16.5	87.2 ± 15.6	0.770£
Pulse median (IQR25-75)	84 (77–96)	88.5 (77–98)	80 (69–88)	0.196&
GCS median (IQR25-75)	15 (13–15)	15 (14–15)	13 (11–15)	**0.013&**
NIHSS < 5 n, (%)	25 (23.8)	24 (28.6)	1 (4.8)	0.022^
NIHSS 5–14 n, (%)	67 (63.8)	54 (64.3)	13 (61.9)	0.839^
NIHSS > 14 n, (%)	13 (12.4)	6 (7.1)	7 (33.3)	**0.004***
Anticoagulant use n, (%)				
DOAC	10 (9.5)	10 (11.9)	0	0.206*
VKA	6 (5.7)	5 (5.9)	1 (4.8)	1*
Antiplatelet use n, (%)				
Acetylsalicylic acid	32 (30.5)	21 (25)	11 (52.4)	**0.015^**
Clopidogrel	8 (7.6)	7 (8.3)	1 (4.8)	1*

GCS: Glasgow Coma Scale (19), BP: Blood pressure, DOAC: Direct oral anticoagulant, VKA: Vitamin K antagonist, NLR: neutrophil/lymphocyte ratio, NIHSS: National Institutes of Health Stroke Scale, IS: Ischemic Stroke, ICH: Intracranial hemorrhage, CAD: Coronary Artery Disease, CHF: Congestive Heart Failure, INR: International normalized ratio, APTT: Activated partial thromboplastin time, IQR: Interquartile range, SD : Standard deviation

Variables	All (n = 105)	Non-ICH group (n = 84)	ICH group (n = 21)	p value
Blood test levels median (IQR25-75)				
NLR	2.39 (1.57–3.44)	2.44 (1.62–3.82)	2.05 (1.55–2.66)	0.090&
Creatinine (mg/dl)	0.9 (0.76–1.10)	0.89 (0.76–1.11)	0.93 (0.83–1.02)	0.990&
Troponin-T (ng/l) (n = 25)	12 (7–18)	11 (6–18)	20 (17–21)	0.077&
Troponin-I (ng/l) (n = 59)	8.2 (5.35–16.6)	8.25 (5.38–17.3)	8.1 (5.7–15.4	0.984&
INR	1.05 (0.98–1.15)	1.11 (0.99–1.18)	1 (0.93–1.07)	0.011&
APTT (second)	24.6 (22.7–28)	24.7 (23.1–28)	23.6 (21.4–26.3)	0.072&
Dimer (µg/L) (n = 20)	910 (530–2665)	1040 (515–2783)	910 (870–2400)	0.857&

GCS: Glasgow Coma Scale (19), BP: Blood pressure, DOAC: Direct oral anticoagulant, VKA: Vitamin K antagonist, NLR: neutrophil/lymphocyte ratio, NIHSS: National Institutes of Health Stroke Scale, IS: Ischemic Stroke, ICH: Intracranial hemorrhage, CAD: Coronary Artery Disease, CHF: Congestive Heart Failure, INR: International normalized ratio, APTT: Activated partial thromboplastin time, IQR: Interquartile range, SD : Standard deviation

^ Pearson chi-square; * Fisher’s exact test. & Mann-whitney u, £ Student t

Primary Outcome: Association of 0–3-Hour Fibrinogen Decline with 24-Hour ICH

In the overall cohort (n = 105), baseline fibrinogen level was 372 mg/dL (IQR: 292–441). Median baseline fibrinogen was 360 mg/dL (277–437) in the non-ICH group (n = 84) and 404 mg/dL (349–463) in the ICH group (n = 21), with no significant difference between the groups (p = 0.125). CT images were independently reviewed by two emergency medicine specialists who were blinded to the patients’ fibrinogen levels and clinical data. Regarding delta fibrinogen levels, the overall cohort showed a median decrease of 80 mg/dL (19–199). In the non-ICH group, the median change was 48.25 mg/dL (14.5–159), whereas in the ICH group it was markedly higher at 200 mg/dL (62–260). This difference was statistically significant (p = 0.009, Mann-Whitney U test; 95% CI -154- -15). Fibrinogen levels at presentation and delta fibrinogen levels in the ICH and non-ICH groups are presented in Table 2.

Table 2
Fibrinogen measurement of groups

Variable median, (Q1-Q3)	All Group (n = 105)	Non-ICH group (n = 84)	ICH group (n = 21)	p
Fibrinogen levels baseline	372 (292–441)	360 (277–437)	404 (349–463)	0.125 &
Delta fibrinogen levels	80 (19–199)	48.25 (14.5–159)	200 (62–260)	0.009 &
IQR: Interquartile range, &: Mann-Whitney U, Q: Quartile ICH: Intracranial hemorrhage				

In the subgroup analysis, cases of parenchymal hematoma (PH1 and PH2, grouped as PH) were compared to the non-ICH group. A statistically significant difference in delta fibrinogen levels was observed between the PH group and the non-ICH group ($p = 0.03$, Mann–Whitney U test; 95% CI: − 230 to − 36; Bonferroni-corrected). Hemorrhagic infarction cases (HI1 and HI2, grouped as HI) were also compared to the non-ICH group. No statistically significant difference in delta fibrinogen levels was observed between these groups ($p = 0.615$, Mann–Whitney U test; 95% CI: − 94 to 23; Bonferroni-corrected). Radiological subtypes of ICH (HI, PH) were analyzed separately, and findings are summarized in Table 3.

Table 3
Subtype of ICH and fibrinogen measurement

outcome variables median, (IQR25-75)	non-ICH (n = 84)	HI (n = 11)	PH (n = 10)
Fibrinogen levels baseline	360 (277–437)	407 (348–447)	398 (359–459)
Delta fibrinogen levels	48.25 (14.5–159)	97 (41.5–174)	219 (170–331)
HI: Hemorrhagic Infarct, PH: Parenchymal Hematoma, ICH: Intracranial Hemorrhage			

A separate ROC curve analysis was conducted to evaluate the predictive performance of delta fibrinogen levels for identifying PH. The area under the curve (AUC) was 0.748, indicating acceptable discriminative ability (Fig. 2). A cut-off value of 158 mg/dL was determined, resulting in a sensitivity of 74.7% (95% CI: 64.8–83.1) and a specificity of 80.0% (95% CI: 44.4–97.5). The positive likelihood ratio (LR+) for delta fibrinogen in predicting ICH was 3.74 (95% CI: 1.08–12.99), while the negative likelihood ratio (LR–) was 0.32 (95% CI: 0.20–0.51).

Secondary Outcome: Association of Parenchymal Hematoma with 3-Month Functional Outcome

At 3 months, the median (IQR) mRS was 4 (2–6) in the ICH group versus 2 (1–4) in the non-ICH group; the between-group difference was statistically significant (p = 0.033; 95% CI − 2.00 - −1.09). In the subgroup analysis, patients in the PH group had significantly poorer functional outcomes (mRS ≥ 3 at 3

months) compared to the other groups (p = 0.036, 95% CI − 0.288 - −0.0383; Mann–Whitney U test, Bonferroni corrected). There was no statistically significant association between delta fibrinogen value and 3-month functional outcome (p > 0.05).

The group that developed PH also had a significantly higher mortality rate compared to the other groups (p = 0.047, Fisher's exact test).

Discussion

In this study, delta fibrinogen level was shown to be significantly associated with hemorrhagic transformation and PH, whereas baseline fibrinogen levels were not predictive. This finding is consistent with previous studies indicating that the change in fibrinogen level, rather than its initial value, serves as an independent risk factor for tPA-related hemorrhagic transformation or PH. In our diagnostic performance analysis, the delta fibrinogen level demonstrated moderate discriminative ability for predicting hemorrhagic transformation and PH. It showed acceptable sensitivity and specificity. Although delta fibrinogen demonstrated acceptable discriminative ability, it cannot serve as a standalone diagnostic decision marker since its AUC value (< 0.8) indicates only moderate predictive performance.

As the cornerstone and first-line definitive therapy for acute ischemic stroke, tPA—either alone or as bridging treatment before EVT—carries the risk of tPA-related ICH, which remains the most devastating and feared complication of reperfusion therapy. tPA is a serine protease released by endothelial and hepatic cells that becomes catalytically active when bound to fibrin within a thrombus. Activated tPA converts plasminogen into plasmin, leading to the degradation of cross-linked fibrin and dissolution of the clot. During this process, Fibrin Degradation Products (FDPs) are generated as a result of plasmin-mediated fibrin breakdown [13]. These FDPs exert anticoagulant effects by inhibiting fibrin polymerization and impairing platelet function [13, 14].

Previous studies on myocardial infarction and cerebral thrombolysis have demonstrated that an early increase in FDP levels within the first few hours after intravenous tPA administration is associated with a parallel rise in the risk of early bleeding and the development of PH [15]. Although FDP levels could not be measured in our study due to the unavailability of laboratory assays, the observed decrease in fibrinogen levels likely reflects an increase in FDP concentration, supporting the exact pathophysiological mechanism. Another study reported that, following IV tPA administration, a decrease in fibrinogen within 24 hours was associated with the development of PH [14]. Furthermore, persistent fibrinogen depletion beyond the acute phase has been linked to hematoma expansion and ongoing hemorrhagic risk, suggesting that sustained fibrinogen degradation may contribute not only to the onset but also to the progression of parenchymal hematoma. Consistent with the current literature, our findings suggest that as fibrinogen levels decrease, FDP concentration rises, thereby enhancing the anticoagulant effect and increasing the risk of tPA-related ICH. Early fibrinogen depletion is closely linked with symptomatic ICH following reperfusion therapy.

tPA-related hemorrhage can be radiographically classified as PH or HI [16]. The morbidity and mortality associated with tPA-related ICH are more consistent with PH, particularly with the PH2 subtype [17]. According to the literature, 3-month mortality and poor functional outcomes are significantly higher in patients with PH type 2 compared to other subtypes. Considering the clinical relevance and the need for urgent management in patients with PH, we focused our analysis on this group because its prognostic value in terms of both mortality and morbidity is more significant than that of hemorrhagic infarction [16, 17]. Our study showed that patients who developed PH had a statistically significant difference compared to those in the HI or non-ICH groups, particularly in terms of 3-month mortality and functional outcomes, as measured by the mRS. Patients with PH exhibited higher mortality rates and poorer functional recovery (mRS ≥ 3) compared to the other subgroups. These findings are consistent with previous studies in the literature [16–18].

Current guidelines recommend performing a routine cranial CT scan 24 hours after IV tPA administration. Because PH carries a substantial risk for poor functional outcome, identifying reliable early predictors is clinically important. Fibrinogen dynamics may have a potential role in predicting tPA-related ICH. Our findings support the notion that monitoring patients' fibrinogen levels after thrombolysis may be considered an important component of clinical surveillance, as early fibrinogen decline could serve as a useful adjunct in identifying those at increased risk for developing tPA-related ICH within 24 hours.

Limitations and Strengths

This study was conducted in a single tertiary care center with a limited sample size, which may limit generalizability. Fibrin degradation products and other coagulation markers were not measured due to laboratory constraints, and 3-month outcomes were partly assessed via telephone interviews. Despite these limitations, the prospective design, blinded imaging evaluation, and standardized protocol strengthen the reliability and clinical relevance of our findings. Future multicenter studies with larger cohorts and serial biomarker measurements could further clarify the prognostic utility of early fibrinogen kinetics.

Conclusion

Early fibrinogen decline within the first three hours after IV tPA was significantly associated with 24-hour intracranial hemorrhage, particularly parenchymal hematoma. Patients who developed PH had higher mortality and poorer 3-month outcomes. Monitoring early fibrinogen changes may strengthen post-thrombolysis risk prediction and help identify patients requiring closer follow-up.

Abbreviations

ASA
Acetylsalicylic Acid

AUC
Area Under the Curve
CAD
Coronary Artery Disease
CHF
Congestive Heart Failure
CT
Computed Tomography
DM
Diabetes Mellitus
FDPs
Fibrin Degradation Products
GCS
Glasgow Coma Scale
HI
Hemorrhagic Infarction
HI1
Hemorrhagic Infarction Type 1
HI2
Hemorrhagic Infarction Type 2
HT
Hypertension
ICH
Intracranial Hemorrhage
IQR
Interquartile Range
IS
Ischemic Stroke
IV
Intravenous
LR+
Positive Likelihood Ratio
LR–
Negative Likelihood Ratio
MRI
Magnetic Resonance Imaging
mRS
Modified Rankin Scale
NIHSS
National Institutes of Health Stroke Scale

PH
Parenchymal Hematoma
PH1
Parenchymal Hematoma Type 1
PH2
Parenchymal Hematoma Type 2
ROC
Receiver Operating Characteristic
SD
Standard Deviation
SPSS
Statistical Package for the Social Sciences
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology
SWI
Susceptibility-Weighted Imaging
tPA
Tissue Plasminogen Activator
USA
United States of America
EVT
Endovascular Treatment

Declarations

Human Ethics and Consent to Participate

I confirm that I have read the Editorial Policy pages. Marmara University Clinical Research Ethics Committee approved the study protocol (protocol number: 07.2023.903), and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Consent to Participate

Written informed consent was obtained from all participants prior to enrollment.

Consent for publication

Yes

Clinical trial number

N/A

Availability of data and material

The study protocol, predefined statistical analysis plan, and the datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions statement

SB: Conceptualization; Methodology; Data curation; Investigation; Visualization; Project administration; Writing – original draft (lead), Formal analysis.

EK: Conceptualization; Methodology; Data curation; Investigation; Writing – original draft (supporting), Writing- review & editing.

ZK: Conceptualization; Methodology; Data curation; Investigation; Writing – original draft (supporting)

AG: Conceptualization;Methodology; Data curation; Visualization; Writing – original draft (supporting).

AD: Conceptualization; Methodology; Resources; Formal analysis; Supervision; Validation; Project administration; Writing- review & editing.

All authors read and approved the final submitted version of the manuscript.

All authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Figures

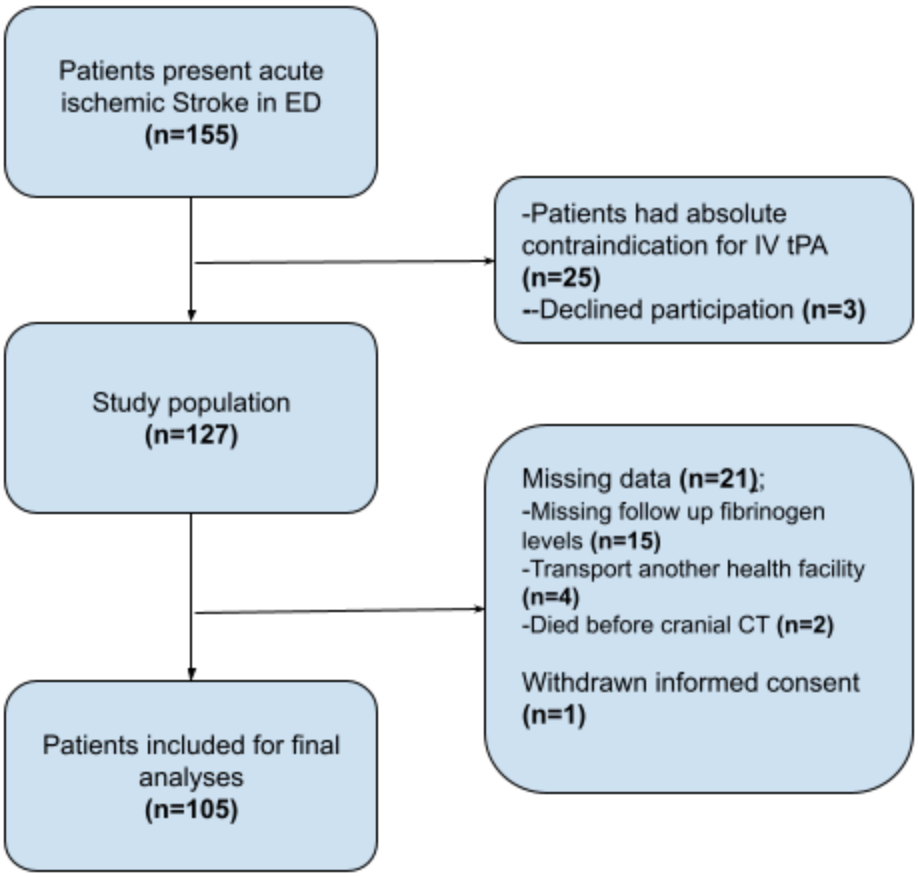


Figure 1

Study Flowchart

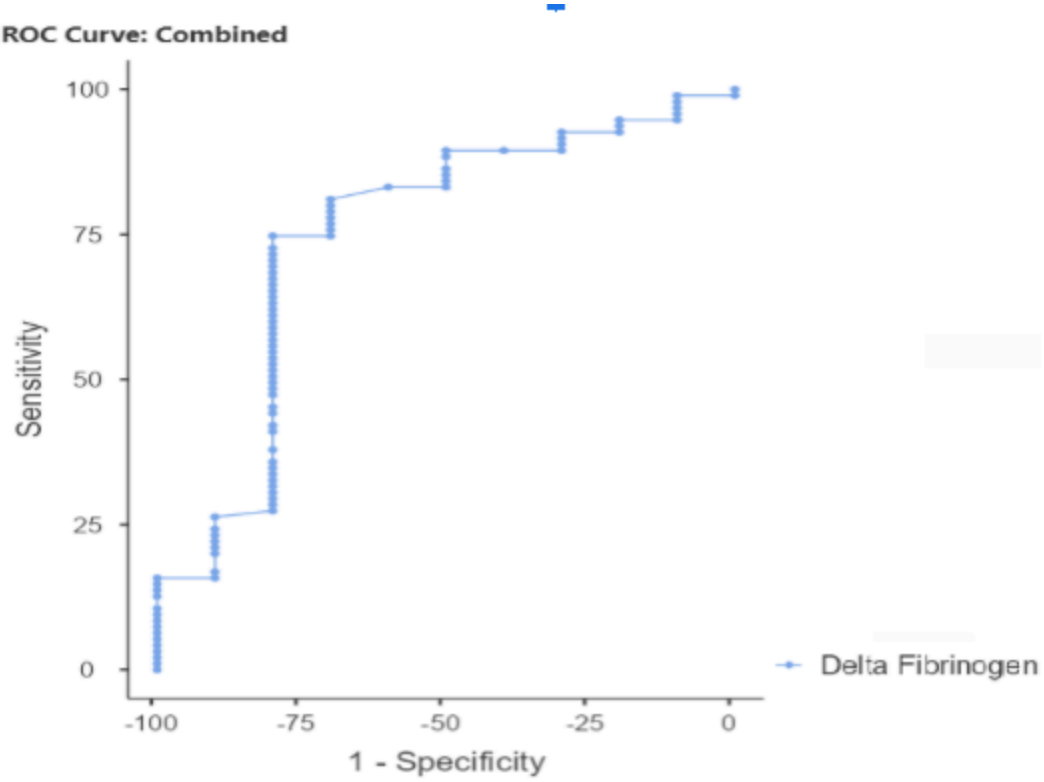


Figure 2

Receiver operating characteristic (ROC) curve of delta fibrinogen for predicting ICH.