

ORIGINAL ARTICLE

Profilin-1 as a Potential Biomarker in Acute Ischemic Stroke: Predictive Value for Large Vessel Occlusion and Mechanical Thrombectomy

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SUMMARY

Background: This study aimed to investigate the diagnostic and prognostic value of serum Profilin-1 (PFN-1) levels in patients with acute ischemic stroke. Ischemic stroke is a serious condition requiring rapid diagnosis and reperfusion therapy (particularly mechanical thrombectomy [MT]). However, appropriate patient selection and accurate determination of symptom onset can be challenging. PFN-1, previously shown to be elevated in other vascular diseases, was clinically investigated for the first time in ischemic stroke through this study.

Methods: This prospective observational study included 152 patients with radiologically confirmed AIS and 66 age- and gender-matched healthy controls. Serum PFN-1 levels were measured upon admission. The study assessed PFN-1 concentrations across subgroups (large vessel occlusion [LVO] presence, MT performed, symptom duration ≤ 6 hours versus > 6 hours) and conducted ROC analyses to determine predictive performance.

Results: PFN-1 levels were significantly higher in stroke patients than in controls ($p < 0.001$). Moreover, PFN-1 levels were markedly elevated in patients with LVO compared to those without ($p < 0.001$), in patients who underwent MT compared to those who did not ($p = 0.003$), and in patients presenting within 6 hours of symptom onset versus those who presented later ($p < 0.001$). Receiver operating characteristic analysis indicated that PFN-1 levels, using specific cutoff values, could predict stroke diagnosis, LVO presence, MT requirement, and the 6-hours symptom window.

Conclusions: These findings suggest that PFN-1 is associated with increased thrombus burden. In conclusion, serum PFN-1 is a readily measurable biomarker with potential utility in the emergency management of IS, assisting in diagnosis, identifying LVO and MT candidates, and estimating symptom duration. However, validation through larger, multicenter studies is warranted.

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KEYWORDS

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INTRODUCTION

Ischemic stroke (IS) is a neurological emergency resulting from a sudden interruption of cerebral blood flow, leading to significant morbidity and mortality. Patient assessment typically relies on clinical scoring systems and neuroimaging techniques. The cornerstone of IS treatment is timely recanalization, achieved through intravenous thrombolysis or mechanical thrombectomy (MT). These interventions aim to salvage the viable brain tissue, termed the “penumbra,” which has reduced perfusion but remains protected from infarction owing to sufficient collateral circulation [1]. Time from symptom onset to treatment is a critical determinant of recanalization therapy response, with shorter intervals correlating with improved efficacy [2].

MT is recognized as the standard reperfusion therapy for acute ischemic stroke (AIS) cases caused by large vessel occlusion (LVO) in the anterior circulation [3]. For patients presenting within 6 hours of symptom onset, computed tomography angiography or magnetic resonance angiography is recommended to assess eligibility and guide selection for MT [4,5]. For patients presenting within 24 hours of symptom onset, perfusion imaging alongside vascular imaging is advised [6,7].

Profilin-1 (PFN-1) is an actin monomer-binding protein expressed in almost all tissues [8] and involved in numerous physiological and pathophysiological processes, including cell migration, morphological structure, cytotoxicity, microtubule polymerization, synaptic plasticity, vascular permeability, angiogenesis, apoptosis, chemoresistance, and oxidative stress response [9]. Prior studies have reported elevated serum PFN-1 levels in cardiovascular conditions such as atherosclerosis, hypertension, and myocardial infarction [10]. However, to our knowledge, only one clinical study has examined serum PFN-1 levels and their clinical associations in patients with IS.

Therefore, this study aimed to investigate the potential relationship between serum PFN-1 levels and diagnostic parameters, therapeutic interventions, and prognostic indicators in patients with AIS.

MATERIALS AND METHODS

Study design and ethical approval

This single-center, prospective observational study was conducted at a tertiary healthcare institution. Ethical approval was obtained from the local ethics committee (Protocol No. SÜKAEK/2023/3/17, Date: 01-03-2023). Patients presenting to the emergency department (ED) with suspected stroke between March and July 2023 were enrolled, along with healthy controls matched for age and gender.

Patient selection

Inclusion criteria were as follows: age ≥ 18 years; admission to the ED due to neurological manifestations, such as altered level of consciousness, speech disturbances, motor or sensory deficits, headache, vertigo, gait instability, imbalance, or visual impairment; symptom onset within the last 24 hours, and radiological confirmed AIS. Exclusion criteria were as follows: age < 18 years; imaging evidence of hemorrhagic stroke (epidural/subdural/parenchymal hematoma or subarachnoid hemorrhage); traumatic brain injury; absence of diffusion restriction on diffusion-weighted magnetic resonance imaging (DW-MRI); comorbidities known to affect PFN-1 levels (e.g., acute coronary syndrome, pulmonary thromboembolism, malignancy, acute renal failure, severe hepatic failure, or sepsis); inability to obtain informed consent from the patient or legal representative.

Control group and data collection

The control group comprised age- and gender-matched healthy volunteers not meeting any of the exclusion criteria who consented to participate. Sociodemographic data, vital signs, comorbidities, presenting symptoms, time from symptom onset, clinical scores (Glasgow Coma Scale [GCS], National Institutes of Health Stroke Scale [NIHSS], Alberta Stroke Program Early CT Score [ASPECTS], and 3-month modified Rankin Scale [mRS]) for the patient group, and sociodemographic characteristics of the control group were recorded using a standardized data collection form.

Sample collection and analyses

Five milliliters of venous blood were drawn from each patient and control into gel-separator tubes. Samples were centrifuged at 4,000 rpm for 10 minutes immediately after collection. Separated plasma aliquots were stored at -80°C until analysis. Plasma PFN-1 levels were measured via enzyme-linked immunosorbent assay (ELISA) using a Human Profilin-1 ELISA Kit (Elabscience Biotechnology Inc., Houston, TX, USA; sensitivity: 46.88 pg/mL; assay range: 78.13 - 5,000 pg/mL). All measurement results were entered into the data collection form.

Treatment management

All patients received standard diagnostic and therapeutic care according to current American Heart Association/American Stroke Association (AHA/ASA) guidelines [4]. NIHSS scores were assessed and symptom onset times determined for all suspected stroke patients. Patients presenting within the 4.5 hours therapeutic window without contraindications received intravenous (IV) alteplase. Patients in whom LVO was detected by CT angiography, or those presenting ≥ 4.5 hours after symptom onset or with “wake-up” stroke, underwent DW-MRI including fluid-attenuated inversion recovery sequences. MT was performed in eligible patients based on imaging and clinical findings.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics (Version 25) and MedCalc (Version 20; Med Calc Software Ltd., Ostende, Belgium). Analyses were conducted at a 95% confidence level. Normality of distribution for continuous variables was assessed by the Kolmogorov-Smirnov test. Descriptive statistics were presented as mean \pm standard deviation for normally distributed variables, median (minimum - maximum) for non-normally distributed variables, and frequency (n) and percentage (%) for categorical variables. Comparisons between two independent groups were made with the Student's *t*-test for normally distributed continuous variables, the Mann-Whitney U test for non-normally distributed continuous variables, and the chi-squared or Fisher's exact test for categorical variables. Receiver operating characteristic (ROC) analysis was performed to evaluate the diagnostic and prognostic value of PFN-1 levels, with determination of optimal cut-off points, sensitivity, specificity, area under the curve (AUC), and 95% confidence intervals. A *p*-value of < 0.05 was considered statistically significant in all analyses.

RESULTS

During the specified period, 288 patients presented to our ED with stroke symptoms. A total of 134 patients met at least one exclusion criterion and were therefore excluded. The study included 152 patients with IS. A control group of 66 healthy volunteers with similar demographic characteristics was also recruited. The overall study cohort thus comprised 218 individuals (Figure 1).

Among the 152 patients with IS, 79 (52%) were female, and the mean age was 72.42 ± 11.10 years. In the control group, 36 (54.5%) were female, and the mean age was 71.55 ± 9.31 years. The patient and control groups were comparable in terms of gender and age ($p > 0.727$ and $p > 0.575$, respectively).

Patients with IS were categorized into two groups: those with LVO (LVO(+)) and those without (LVO(-)). The data obtained are presented in Table 1. Both groups had similar demographic profiles. LVO(+) patients exhibited higher NIHSS scores, lower ASPECT scores, and earlier hospital presentation after symptom onset compared to LVO(-) patients. Additionally, LVO(+) patients had poorer clinical outcomes, as assessed via 3-month mRS, and higher mortality rates.

Among the 152 patients with IS, 14 (9.2%) received IV thrombolytics alone, 41 (27%) underwent MT alone, 35 (23%) received both IV thrombolytics and MT, and 62 (40.8%) were treated with antiplatelet therapy only.

Patients were further grouped into those who underwent MT(+) and those receiving medical treatment only MT(-) and compared. The data obtained are presented in Table 1. Both groups had similar demographic characteristics. MT(+) patients demonstrated higher NIHSS

scores, lower ASPECT scores, shorter symptom-to-presentation times, worse clinical outcomes, and higher mortality compared to MT(-) patients (Table 1).

When serum PFN-1 levels were compared between the study groups, the median serum PFN-1 level in the patient group was 4,010.15 pg/mL (range 286.4 - 5,001 pg/mL) compared to 1,919 pg/mL (range 276 - 5,001 pg/mL) in the control group. Serum PFN-1 levels were significantly higher in the patient group compared to the controls ($p < 0.001$). The median serum PFN-1 level was 4,570.85 pg/mL in LVO(+) patients compared to 2,259.60 pg/mL in LVO(-) patients. Accordingly, PFN-1 levels were significantly higher in LVO(+) patients ($p < 0.001$). The median serum PFN-1 level was 4,508.35 (557.1 - 5,001) pg/mL in MT(+) patients compared to 2,827.05 (286.4 - 5,001) pg/mL in MT(-) patients. Accordingly, PFN-1 levels were significantly higher in MT(+) patients ($p = 0.003$) (Table 2).

Serum PFN-1 levels were also analyzed with regard to the time from symptom onset to hospital presentation. The median serum PFN-1 level in patients presenting within 6 hours was 4,714.4 (286.4 - 5,001) pg/mL, compared to 2,012 (347 - 5,001) pg/mL in those presenting after 6 hours. Accordingly, serum PFN-1 levels were significantly higher in patients presenting within 6 hours ($p < 0.001$) (Table 2).

The discriminative ability of PFN-1 levels at presentation among patient subgroups was evaluated via ROC analysis. The results obtained are presented in Table 3. Accordingly, serum PFN-1 levels of $> 3,669.02$ pg/mL were able to identify patients with IS with 54.61% sensitivity and 89.39% specificity (AUC = 0.733; 95% CI = 0.669 - 0.791; $p < 0.001$). In addition, serum PFN-1 levels of $> 2,358$ pg/mL identified LVO(+) patients within the IS group with 85.37% sensitivity and 51.43% specificity (AUC = 0.667; 95% CI = 0.586 - 0.741; $p < 0.001$) (Figure 2). Furthermore, serum PFN-1 levels of $> 2,143.1$ pg/mL identified MT(+) patients within the IS group with 86.84% sensitivity and 44.74% specificity (AUC = 0.638; 95% CI = 0.556 - 0.714; $p = 0.002$). When evaluated by symptom duration, serum PFN-1 levels of $> 2,480.2$ pg/mL identified patients with IS with symptom duration ≤ 6 hours with 81.73% sensitivity and 68.75% specificity (AUC = 0.753; 95% CI = 0.677 - 0.819; $p < 0.001$) (Figure 2).

DISCUSSION

PFN-1 levels have previously been evaluated in numerous pathological conditions and have recently been identified as a parameter of interest in occlusive vascular clinical settings. The present study aimed to clinically assess serum PFN-1 levels in IS patients for the first time in literature. The results show that serum PFN-1 levels were significantly elevated in patients with IS compared to the control group, in LVO(+) patients compared to LVO(-) patients, and MT(+) patients compared to MT(-) patients. Additionally, PFN-1 levels

Table 1. Clinical features of patients with ischemic stroke.

Properties/Variables	LVO(+) (n = 82)	LVO(-) (n = 70)	P	MT(+) (n = 76)	MT(-) (n = 76)	P
Age (years), mean ± SD	72.24 ± 11.82	70.23 ± 10.26	0.441	71.04 ± 11.15	73.80 ± 10.94	0.125
Gender, n (%)						
Female	45 (54.9)	34 (48.6)	0.438	39 (51.3)	40 (52.6)	0.871
Male	37 (45.1)	36 (51.4)		37 (48.7)	36 (47.4)	
Comorbidities, n (%)						
Diabetes Mellitus (+)	28 (34.1)	29 (41.4)	0.355	27 (35.5)	30 (39.5)	0.615
Hypertension (+)	63 (78.6)	58 (82.9)	0.358	59 (77.6)	62 (81.6)	0.546
Heart failure (+)	8 (9.8)	10 (14.3)	0.389	8 (10.5)	10 (13.2)	0.616
Atrial fibrillation (+)	24 (29.3)	20 (28.6)	0.925	22 (28.9)	22 (28.9)	1.000
HR (+)	24 (29.3)	25 (35.7)	0.397	24 (31.6)	25 (32.9)	0.862
CRF (+)	0 (0)	4 (5.7)	0.043	0 (0.0)	4 (5.3)	0.120
Vital signs, median (min-max)						
SBP (mmHg)	160 (89 - 240)	157.5 (100 - 210)	0.730	160 (100 - 240)	157 (89 - 210)	0.281
DBP (mmHg)	90 (60 - 130)	90 (52 - 120)	0.318	90.5 (60 - 130)	90 (52 - 120)	0.103
MAP (mmHg)	113.33 (73.33 - 160)	110 (72.33 - 150)	0.451	113.33 (73.33 - 160)	109.67 (72.33 - 150)	0.140
Pulse (beats/minute)	85 (46 - 120)	87 (58 - 124)	0.339	85 (46 - 120)	87 (58 - 124)	0.519
Body temperature (°C)	36.5 (36.2 - 37.2)	36.4 (36 - 38)	0.010	36.5 (36.2 - 37.2)	36.4 (36 - 38)	0.019
Respiratory rate (/minute)	14 (10 - 24)	14 (11 - 22)	0.012	15 (10 - 24)	14 (11 - 22)	0.009
Symptoms, n (%)						
Plegia (+)	71 (86.6)	44 (62.9)	< 0.001	66 (86.8)	49 (64.5)	0.002
Impaired consciousness (+)	29 (35.4)	10 (14.3)	0.003	25 (32.9)	14 (18.4)	0.041
Dysarthria (+)	19 (23.2)	30 (42.9)	0.010	19 (25.0)	30 (39.5)	0.056
Aphasia (+)	18 (22)	12 (17.1)	0.458	14 (18.4)	16 (21.1)	0.684
Vertigo (+)	4 (4.9)	18 (25.7)	< 0.001	1 (1.3)	21 (27.6)	< 0.001
Symptom duration (hour) median (min-max)	5 (1 - 16)	5.25 (1 - 22)	0.008	5 (1 - 14)	5 (1 - 22)	0.006
Clinical scores, median (min-max)						
GCS	12 (6 - 15)	14 (8 - 15)	0.001	12 (8 - 15)	13.5 (6 - 15)	0.097
NIHSS	14 (6 - 24)	7 (1 - 21)	< 0.001	14 (6 - 24)	7 (1 - 21)	< 0.001
ASPECTS	8 (4 - 10)	9 (5 - 10)	0.007	8 (4 - 10)	9 (5 - 10)	0.025
3rd month mRS, n (%)						
Good clinical outcome (mRS = 0 - 2)	36 (43.9)	48 (68.6)	0.002	34 (44.7)	50 (65.8)	0.009
Poor clinical outcome (mRS = 3 - 6)	46 (56.1)	22 (31.4)		42 (55.3)	26 (34.2)	
3-month mortality, n (%)						
Mortality (+)	21 (25.6)	3 (4.3)	< 0.001	20 (25.6)	4 (4.3)	< 0.001
Mortality (-)	61 (74.4)	67 (95.7)		56 (73.7)	72 (94.7)	

LVO(+) Those with major vessel occlusion, LVO(-) Those without major vessel occlusion, MT(+) Those with mechanical thrombectomy, MT(-) Those without mechanical thrombectomy, CAD Coronary Artery Disease, CRF Chronic Renal Failure, SBP Systolic Blood Pressure, DBP Diastolic Blood Pressure, MAP Mean Arterial Pressure, GCS Glasgow Coma Scale, NIHSS National Institutes of Health Stroke Scale, ASPECTS Alberta Stroke Program Early CT Score, HR Heart Rate.

Table 2. Comparison of serum Profilin-1 levels.

Groups	PFN-1 (pg/mL), median (min-max)	p
Patient group (n = 152)	4,010.15 (286.4 - 5,001)	< 0.001
Control group (n = 66)	1,919 (276 - 5,001)	
LVO(+) (n = 82)	4,570.85 (557.1 - 5,001)	< 0.001
LVO(-) (n = 70)	2,259.60 (286.1 - 5,001)	
MT(+) (n = 76)	4,508.35 (557.1 - 5,001)	0.003
MT(-) (n = 76)	2,827.05 (286.4 - 5,001)	
Symptom duration ≤ 6 hours (n = 104)	4,714.4 (286.4 - 5,001)	< 0.001
Symptom duration > 6 hours (n = 48)	2,012 (347 - 5,001)	

PFN-1 Serum Profilin-1 level, LVO(+) Patients with large vessel occlusion, LVO(-) Patients without large vessel occlusion, MT(+) Patients with Mechanical Thrombectomy, MT(-) Patients without Mechanical Thrombectomy.

Table 3. ROC Analyses of serum Profilin-1 levels.

	Cutoff value	AUC	95% CI	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	p
Diagnosis	> 3,669.02	0.733	0.669 - 0.791	54.61	89.39	92.2	46.1	< 0.001
LVO(+)	> 2,358	0.667	0.586 - 0.741	85.37	51.43	67.3	75.0	< 0.001
MT(+)	> 2,143.1	0.638	0.556 - 0.714	86.84	44.74	61.1	77.3	0.002
Symptom duration ≤ 6 hours	> 2,480.2	0.753	0.677 - 0.819	81.73	68.75	85	63.5	< 0.001

AUC Area under ROC curve, 95% CI 95% confidence interval, PPV positive predictive value, NPV negative predictive value, LVO(+) patients with large vessel occlusion, MT(+) patients undergoing mechanical thrombectomy.

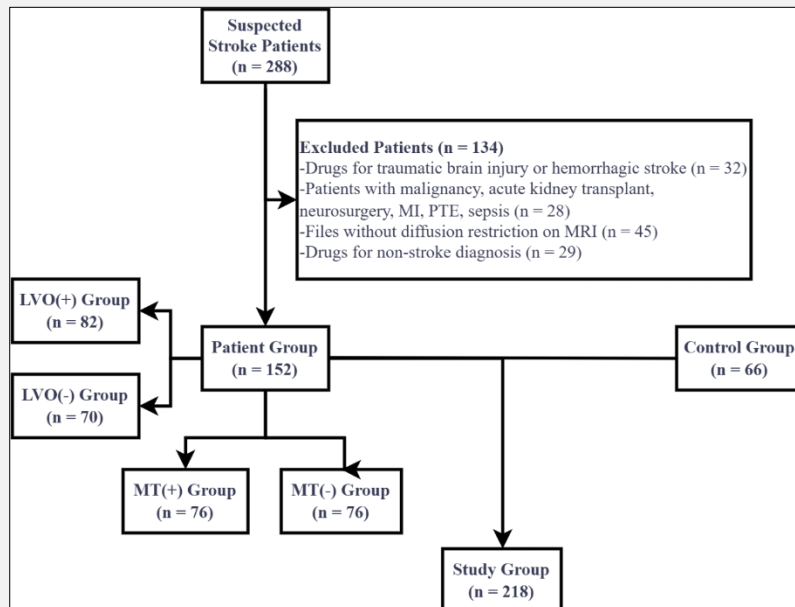


Figure 1. Study Flowchart (MI Myocardial infarctus, PTE Pulmonary thromboembolism, LVO Large vessel occlusion, MT Mechanical thrombectomy).

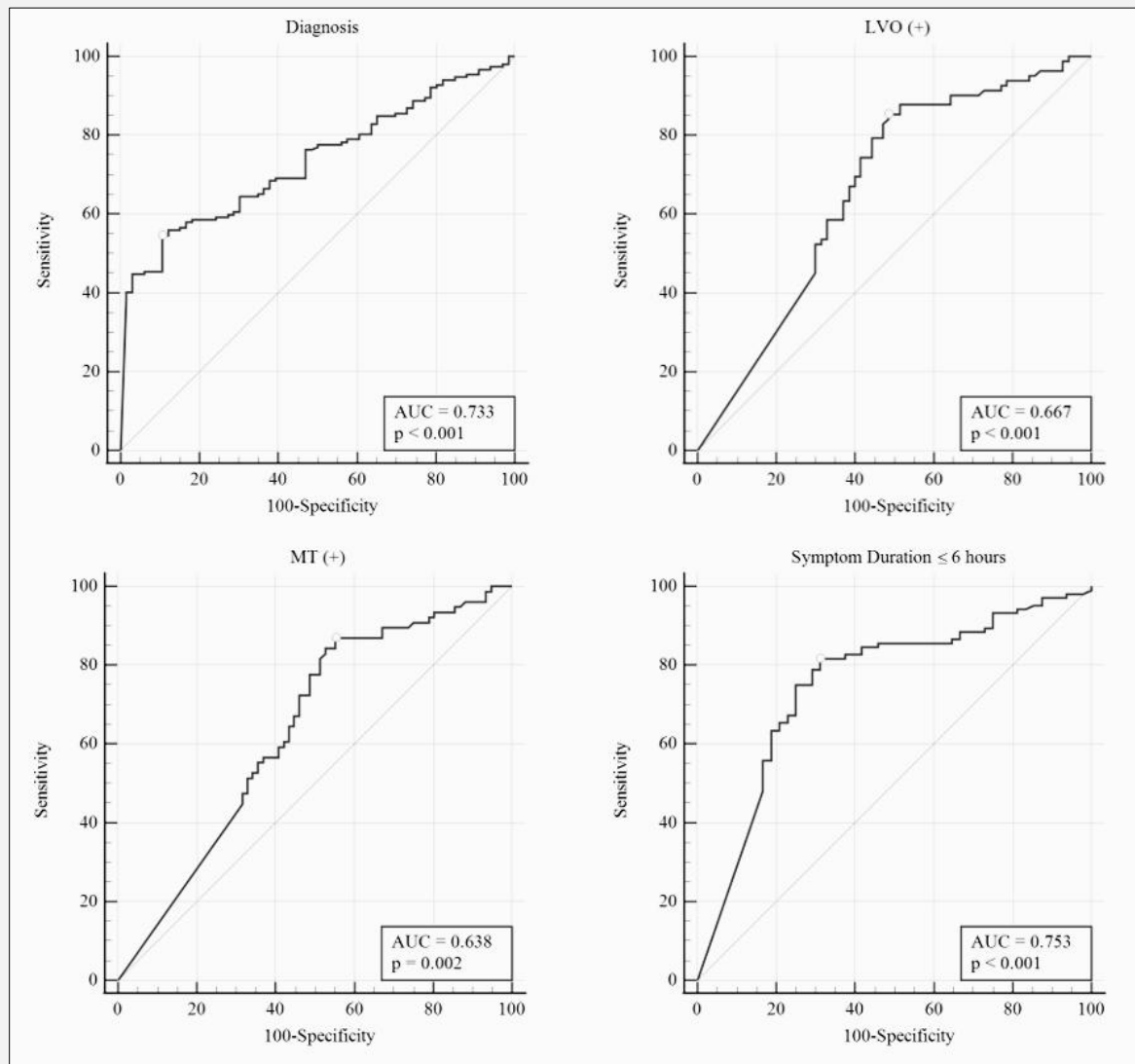


Figure 2. ROC curves demonstrating the discriminatory ability of PFN-1 measurements in identifying LVO(+) and MT(+) patients among individuals with ischemic stroke (LVO(+) Patients with large vessel occlusion, MT(+) Patients who underwent mechanical thrombectomy, AUC Area under the ROC curve).

were significantly higher in patients presenting within the first 6 hours of symptom onset compared to those presenting later. Moreover, we demonstrated that serum PFN-1 level, based on the cutoff values identified, serves as a valuable biomarker for diagnosing stroke, predicting LVO, and estimating symptom duration. In this context, our study is the first clinical investigation of its kind. We believe the results will contribute significantly to the literature.

PFN-1 is an actin-binding protein involved in atherosclerosis, smooth muscle cell proliferation, regulation of the microfilament system, and signaling pathways in

mesenchymal cells [11]. Elevated PFN-1 levels have been reported in atherosclerosis, myocardial infarction, hypertension, diabetes, pulmonary thromboembolism, and certain cancers [10,12-14]. Lu et al. demonstrated increased PFN-1 expression in microglial cells from the ischemic penumbra cortex following middle cerebral artery occlusion in a murine model [9]. The present study confirms that serum PFN-1 levels are elevated in patients with IS, corroborating these experimental observations. Furthermore, unlike prior work, our study is the first to report these data in a clinical stroke cohort. In IS, high thrombus burden is linked to LVO [15] and

is associated with increased stroke severity, treatment complications, and poor clinical outcomes [16]. Ramaiola et al. reported elevated PFN-1 levels in thrombus material from acute myocardial infarction patients, suggesting that PFN-1 increases with platelet accumulation in coronary thrombi [11]. Similarly, Paszek et al. observed elevated serum PFN-1 levels in myocardial infarction patients [17]. In this study, patients with LVO exhibited significantly higher serum PFN-1 levels (Table 2). Although the precise mechanism remains to be elucidated, we hypothesize that the elevated PFN-1 in LVO(+) stroke patients reflects their greater thrombus burden.

The time from symptom onset is one of the most important determinants of response to endovascular and thrombolytic treatment in AIS. As the symptom-to-treatment interval shortens, the likelihood that patients will benefit from endovascular and thrombolytic therapies increases. This is largely because, without successful recanalization, the volume of the ischemic penumbra decreases over time [18]. Studies have demonstrated that endovascular thrombectomy within the first 6 hours significantly outperforms standard medical care in patients with LVOs of the proximal anterior circulation arteries [1,19]. Paszek et al. identified an inverse relationship between thrombus age and serum PFN-1 levels, attributing this phenomenon to thrombus degradation triggered by fibrinolytic mechanisms [17]. MT is recommended for patients with IS with LVOs presenting within ≤ 6 hours of symptom onset [4]. The present study revealed significantly higher serum PFN-1 levels in patients presenting within this 6-hours window compared to those presenting later. Furthermore, a PFN-1 cutoff value of $> 2,480.2$ pg/mL predicted a symptom duration ≤ 6 hours with 81.73% sensitivity and 68.75% specificity. These findings suggest that serum PFN-1 may aid in estimating symptom duration in LVO patients with unclear symptom onset timelines.

MT has emerged in recent years as a therapy that reduces mortality and morbidity in patients with IS. Compared to medical therapy, endovascular treatment in AIS leads to improved long-term functional independence, health-related quality of life, and cognitive outcomes [20]. Consistent with the literature, the data obtained in the present study showed lower 3-month morbidity and mortality rates in MT-treated patients compared to those receiving medical therapy alone.

The NIHSS is a clinical scoring tool for assessing stroke severity and prognosis. Compared to other scoring systems, NIHSS is the most practical for predicting LVOs in emergency settings [21]. Aligning with existing evidence, our results confirmed higher NIHSS scores in LVO(+) patients and MT(+) patients.

Limitations

The primary limitations of this study include its single-center design and relatively limited sample size. Additionally, PFN-1 levels were measured only at presentation; serial measurements were not performed, which

represents another limitation.

CONCLUSION

Serum PFN-1 levels may represent a valuable and easily obtainable biomarker for diagnosing IS, predicting LVO, assessing the need for MT, and estimating symptom onset timing. However, our findings require validation through larger, multicenter studies incorporating serial PFN-1 measurements.

Ethical Approval:

This study was approved by the Samsun University Clinical Research Ethics Committee on March 1, 2023 (Decision No: SÜKAEK/2023/3/17).

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