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Assessment of the Diagnostic Value of Plasma Level of Von Willebrand Factor and ADAMTS13 in Patients with Cerebral Infarction

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Abstract

Background: Von Willebrand Factor (VWF) is a large multimeric plasma glycoprotein that plays an important role in primary haemostasis. VWF together with ADAMTS13 plays a key role in arterial thrombosis. VWF is integral for platelet adhesion to collagen fibres and atherosclerotic plaues and platelets aggregation under high shear conditions. Upon vascular wall damage, plasma VWF binds to collagen in the exposed endothelial matrix and platelet glycoprotein triggers platelet aggregation and thrombous formation. In the early stages of acute ischaemic stroke, VWF increased significantly and the ADAMTS13 level decreased. The increase of plasma VWF and FVIII in a patient with ischaemic stroke indicated an increased risk of complications and severe neurological deficit. **Objective:** to evaluate the validity of VWF and ADFAMTS13 as diagnostic markers of cerebral infarction by comparing the two markers' validity in diagnosis. **Methods:** this case control study enrolled 38 cerebral infarction patients 20 acute infarction and 18 recurrent infarction. Patients were compared with 65 age and sex with control patients. We performed the VWF assay using the minividas immunofluorescence technique and the ADAMTS13 assay using the ELISA technique. **Results:** VWF level of acute infarction patients (280.97 ± 109.83 IU/dl) while its level in recurrent infarction (264.93 ± 172.8 IU/dl) were highly significantly increased compared to control (75.8 ± 16.24 IU/dl). ADAMTS13 level of acute infarction patients was (506.11 ± 225.24 ng/dl) and (1386.03 ± 667.64 ng/dl) in recurrent infarction patients with highly significant differences between the acute and control group and non-significant different between recurrent and control. ADAMTS13 is an excellent diagnostic test in acute cerebral infarction but a weak diagnostic test in recurrent cerebral infarction but it is a good diagnostic test in differentiation between acute and recurrent cerebral infarc-

tion patients. VWF is an excellent diagnostic test in both acute and recurrent cases. In acute infarction, VWF is positively correlated with kidney function while ADAMTS13 level did not correlate with different laboratory parameters in recurrent infarction. A positive correlation is present between ADAMTS13 and PT & PTT concentration. No correlation exists between VWF & ADAMTS13 in the 3 groups. **Conclusion:** ADAMTS13 is closely related to the occurrence, development and progression of acute cerebral infarction, protecting the brain from ischaemic reperfusion injury. It is an excellent diagnostic test in acute cerebral infarction but a weak diagnostic test in recurrent cerebral infarction while VWF is an excellent diagnostic test in acute & recurrent cerebral infarction. ADAMTS13 is expected to become a new therapeutic agent in acute cerebral infarction patients.

Keywords

VWF, ADAMTS13, Cerebral Infarction

1. Introduction

Von Willebrand Factor (VWF) is a large multimeric plasma glycoprotein that plays an important role in primary haemostasis [1].

VWF together with ADMTS13 plays a key role in arterial thrombosis [2].

Deepening the role of the VWF-ADMTS13 axis in ischaemic brain injury could herald the use of novel therapies such as recombinant ADAMTS13 to reduce infarct size in an acute cerebral ischaemic presentation, reduce the risk of recurrence and improve clinical outcome [3].

There is no clear consensus about whether any marker of haemostasis can be used to predict clinical outcomes post-stroke [4].

Upon vascular wall damage, plasma Von Willbrand Factor binds to collagen in the exposed endothelial matrix and platelet glycoprotein triggers platelet aggregation and thrombous formation [5].

National instate of health stroke scores were used to asses stroke severity presenting median VWF antigen/ADAMTS13 ratio was 2.42 (range 0.78 - 9.53) [6].

Transient ischemic attack (TIA) is the term used to describe a focal neurological deficit caused by vascular illness that resolves in less than 24 hours. A TIA that lasts longer than this is referred to as an infarction or haemorrhage. When a neurological impairment lasting more than 24 hours fully recovers after 3 weeks. This condition is known as a reversible ischemic neurological impairment (RIND). It is hypothesised that this condition is caused by prolonged ischemia that is not severe enough to cause an infarction [7]. Increased VWF can raise the risk of an ischemic stroke when plasma ADAMTS13 levels are low [8].

The level of ADAMTS13 dropped and VWF dramatically increased in the early stages of acute ischemic stroke. Patients with ischemic stroke had higher levels of plasma VWF and FVIII, which suggested a higher risk of sequelae and

severe neurological damage [9].

Through its proteolysis of VWF, ADAMTS13 is discovered to be able to lower the permeability of the brain barrier and regulate the inflammatory response in intracrebral haemorrhage *in vivo* investigations [10].

According the results obtained in previous studies, VWF not only contributes to blood clotting and is important in thrombosis but also mediates inflammatory reactions, modifies vascular permeability, and worsens the progression of the disease. For the prevention and treatment of ischemic stroke, VWF offers a good target [11].

2. Material

This study was conducted on 48 subjects at Al Zahraa University Hospital. Patients were selected from the outpatient clinic of Internal Medicine at Al Zahraa University Hospital in the period from 1/3/2020 to 1/8/2022. Subjects were divided as follows:

The present study was carried out on 48 participants at the Al Zahraa University Hospital. During the period from 1/3/2020 to 1/8/2022, patients were chosen from the Internal Medicine outpatient clinic at Al Zahra University Hospital. Following is the breakdown of the subjects:

Patient group: 38 cerebral infarction patients 20 acute and 18 recurrent (60 - 70 years) 25 females and 13 males.

Control group: They are 65.5 age and sex-matched (5 females and 5 males).

Exclusion criteria include:

- Patients who were diagnosed with other diseases at any time period or previously exposed to anticoagulates.

Ethical consideration:

Patients' free and voluntary written informed consent was obtained as part of this study, which takes into account the fundamental biomedical ethical concept for participant patients. Guardians were made aware of their unrestricted right to participate or withdraw from the study at any point. The confidentiality of rectified data is protected, as well as individual privacy.

Methods

The following was performed for all subjects.

Clinical assessment: (full family history and through clinical examination).

Laboratory tests

Complete blood picture using Beckman counter Hmxhaematology analyses. Liver function test (Billirubin total and direct albumin, protein) kidney function test (urea and creatinine) using unicel DXC600 Synchron Clinical system

Coagulation profile (PT and PTT) using DiAcheck-Cl.

C-reactive protein using latex agglutination test.

Sample collection

For each case, 10 ml of venous blood was withdrawn under complete aseptic condition. 1.8 ml was added to 200 ul 3.2% trisodium citrate (32 g/l) and centri-

fuged at 100 g/20mins, for plasma separation (for PT, PTT, VWF, ADAMTS13) 2 ml was added to ethylene diamine tetracetic acid salts (EDTA) at concentration of 1.2 mg/ml for a complete blood count.

6 ml was left to clot for 30 min at room temperature before centrifugation for 20 min at 300/20min, for serum separation for biochemical assay and CRP.

Automated quantitative test using

Enzyme-linked fluorescent assay technique is used to measure Von Willebrand Factor (VWF) in which the two-step enzyme immunoassay Sandwich method with a final fluorescent detection in used (ELFA) solid phase receptacle (SPR) serves as solid phase as well as a pipetting device for the assay.

Enzyme linked immunosorbent assay (ELISA) for quantitative detection of human A Disintegrin and Metalloproteinase with thrombospondin Motifs 13 (ADAMTS13) which is Sandwich technique.

Biochemical test using automated chemistry analyser.

Coagulation profile (PT and PTT)

C-reactive protein (CRP using qualitative and quantitative agglutination test).

Statistical Analysis

Statistical package for social sciences (SPSS) version 26 was utilized to code and enter the data (IBM Corp Armonk, NY USA).

Descriptive Statistics

For quantitative data, the mean, standard deviation, median, minimum, and maximum were used; for categorical data, frequency (count) and relative frequency (%) were used.

$$\text{Mean} = \sum x/n$$

where Σ = sum and n = number

Standard deviation:

Formula

$$s = \sqrt{\frac{\Sigma\left(X - \bar{x}\right)^2}{n-1}}$$

Explanation

s = sample standard deviation;

Σ = sum of…;

X = each value;

$\bar{x}$ = sample mean;

n = number of values in the sample.

Analytical Statistics

Mann Whitney Test (U test) was used in order to compare two study groups using numerical but non-parametric variables.

Chi-Square test (c2) was applied to compare categorical data. When the anticipated frequency is less than 5, an exact test was utilized in its place.

The correlation between two numerical parameters within the same group was evaluated using Spearman correlation coefficients.

Less than 0.05 was regarded as statistically significant for all parameters when calculating the likelihood of being by chance (P-value).

The P value was considered significant as the following:

$P \geq 0.05$: Non significant.

$P < 0.05$: Significant.

$P \leq 0.001$: Highly significant.

3. Results

The parameters of the patients are summarized in Table 1.

Acute cerebral infarction is the significantly lower mean of RBCs than the recurrent infarction group and control group and the differences between groups are statistically significant (post hoc analysis). However, WBCs, Hb, Platelets means are not statistically difference among the 3 groups. Comparison between groups as regards coagulation profile is summarized in Table 2.

Table 1. Comparison between groups as regard complete blood count.

	Group A (N = 20)		Group B (N = 18)		Group C (control) (N = 10)		P value
	Mean	SD	Mean	SD	Mean	SD	
RBCs ($\times 10^6$ µl)	3.51	0.32	4.43	0.69	4.99	0.44	<0.001
WBCs ($\times 10^3$ unit)	11.69	3.06	12.48	4.36	9.83	0.68	0.145
Hb (gm/dl)	11.61	2.30	11.38	2.86	11.98	1.00	0.813
Platelet ($\times 10^3$ µl)	261.67	151.65	299.22	157.37	359.50	37.30	0.112
Post hoc pair wise comparisons (comparison between each 2 groups)							
		A vs. B		A vs. C		B vs. C	
RBCs ($\times 10^6$ µl)		<0.001 HS		<0.001 HS		0.025 S	

Table 2. Comparison between groups as regard coagulation profile.

	Group A		Group B		Group C (control)		P value
	Mean	SD	Mean	SD	Mean	SD	
PT (sec)	13.91	4.38	13.61	3.19	13.22	0.33	0.875 NS
Conc. (%)	76.24	20.66	79.13	11.52	95.64	3.15	0.007 S
INR	1.25	0.32	1.24	0.31	1.26	0.13	0.992 NS
PTT (sec)	40.19	9.51	42.59	10.94	30.40	3.95	0.006 S
Post hoc pair wise comparisons (comparison between each 2 groups) as regard PT concentration.							
		A vs. B		A vs. C		B vs. C	
PT conc. (%)		1.000		0.007		0.033	
Post hoc pair wise comparison as regard PTT concentration.							
		A vs. B		A vs. C		B vs. C	
PTT (sec)		1.000		0.027		0.006	

Our study shows that significant difference between the studied group as regards prothrombin concentration and PTT and non-significant differences as regards PT time and INR. Comparison between groups as regards liver function showed in (Table 3).

This highly significant difference between the studied groups and control as regards bilirubin level and serum albumin, significant difference as regards protein level between recurrent group and control. As regards kidney function and CRP Table 4, there is highly significant difference between the studied groups and control.

Comparison between the studied groups as regards VWF and ADAMTS13 is summarized in Table 5.

Table 3. Comparison between groups as regards liver function.

	Group A		Group B		Group C (control)		P value
	Mean	SD	Mean	SD	Mean	SD	
Total bilirubin (mg/dl)	0.71	0.47	1.20	0.72	0.5	0.09	0.003 HS
D. blirubin (mg/dl)	0.49	0.42	0.79	0.66	1.72	0.1	0.004 HS
Total protein (g/dl)	5.95	0.69	6.37	1.16	5.39	0.28	0.033 S
Serum albumin (g/dl)	3.10	0.73	2.52	1.10	3.83	0.24	0.003 HS
Post hoc pair wise comparisons (comparison between each 2 groups)							
	A vs. B		A vs. C		B vs. C		
Total bilirubin (mg/dl)	0.025 S		0.17 NS		<0.001 HS		
D. blirubin (mg/dl)	0.368 NS		<0.001 HS		<0.001 HS		
Total protein (g/dl)	0.725 NS		0.430 NS		0.029 S		
Serum albumin (g/dl)	0.06 NS		0.004 HS		0.002 HS		

Table 4. Comparison between the three groups as regards kidney function and CRP.

	Group A	Group B	Group C (control)	P value
Serum creatinine (mg/dl)				
Median	2.1	1.8	0.8	0.000
Range	0.3 - 4.1	3.0 - 3.5	0.2 - 1	HS
Serum urea (mg/dl)				
Median	50.8	60.6	30	0.001
Range	18 - 80	20 - 100	20 - 40	HS
CRP (IU/ml)				
Median	55.5	100.5	3.5	0.000
Range	20 - 100	30 - 150	1.5 - 5.1	HS
Post hoc pair wise comparisons (comparison between each 2 groups)				
	A vs. B	A vs. C	B vs. C	
Serum creatine	0.68 NS	<0.001 HS	<0.001 HS	
Serum urea	0.135 NS	0.073 NS	0.002 NS	
CRP	0.048 NS	0.001 HG	<0.001 HS	

Our study shows a highly significant difference between the two studied groups and control as regards VWF factor and ADAMTS13 and a non-significant difference between the two studied groups and VWF factor. ROC curve showed that ADAMTS13 is an excellent diagnostic test in acute infarction with 100.9% sensitivity and 100% specificity (Figure 1).

While VWF is an excellent diagnostic test in acute and recurrent infarction (Figure 2 & Figure 3) with a sensitivity of 100% and specificity of 80%.

Table 5. Comparison between groups as regard VWF and ADAMTS13.

	Group A		Group B		Group C (control)		P value
	Mean	SD	Mean	SD	Mean	SD	
VWF (IU/dl)	280.97	109.83	264.93	172.05	75.80	16.24	<0.001 HS
ADAMTS13 (ng/dl)	506.11	225.24	1386.03	667.64	1383.51	168.38	<0.001 HS
Post hoc pair wise comparisons (comparison between each 2 groups)							
	A vs. B		A vs. C		B vs. C		
VWF	0.633 NS		<0.001 HS		0.001 HS		
ADAMTS13	<0.001 HS		<0.001 HS		0.429 NS		

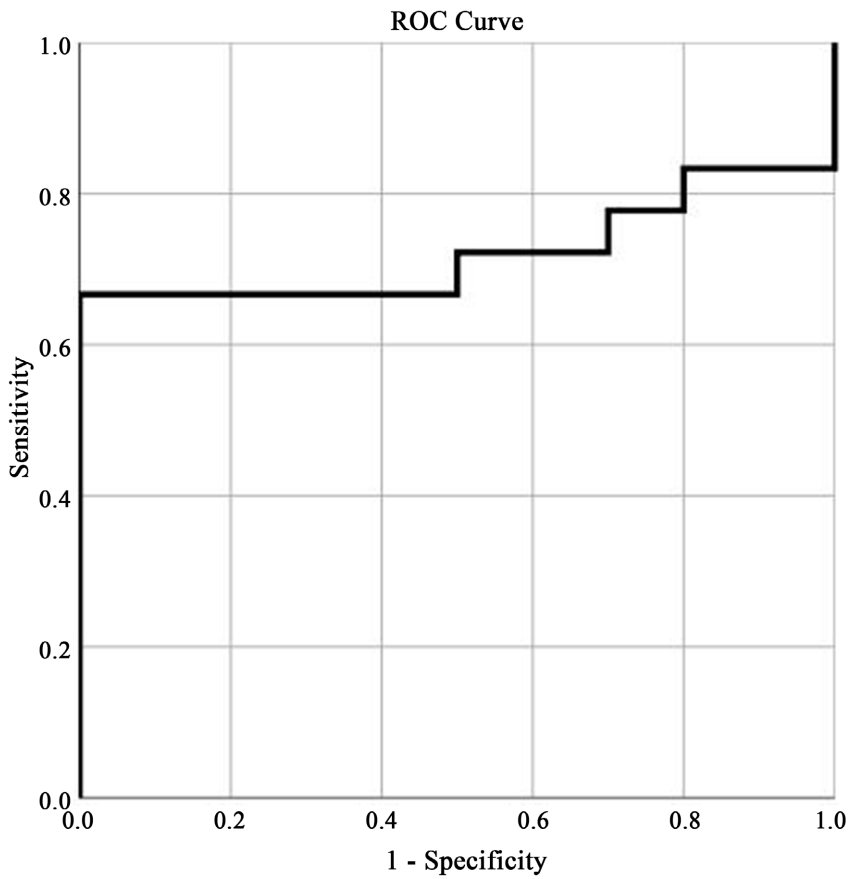

Figure 1. Roc curve of ADAMTS13 in diagnosis of acute cerebral infarction versus control.

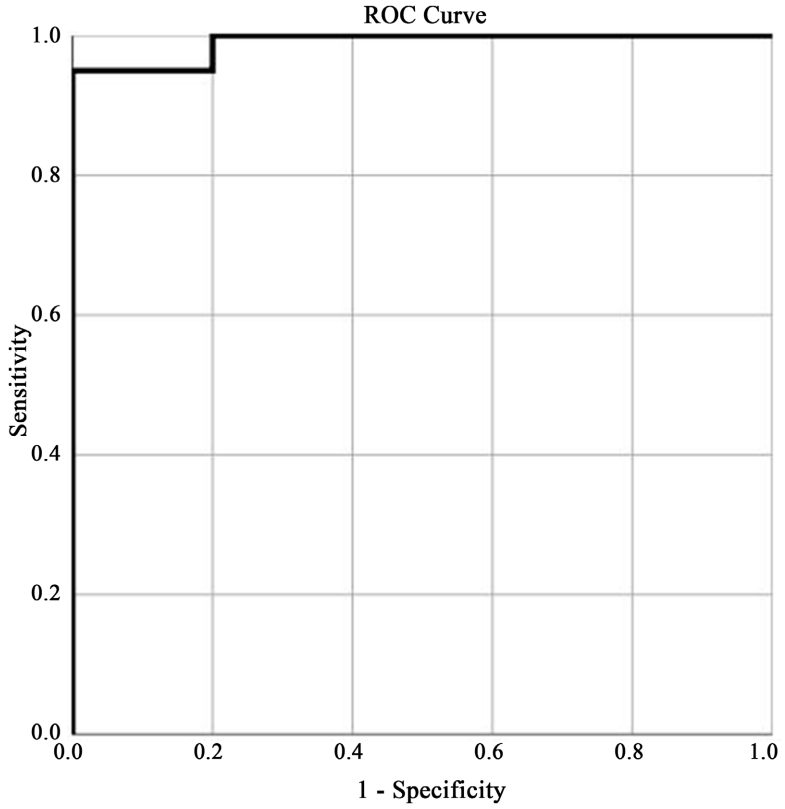

Figure 2. Roc curve of VWF in diagnosis of acute cerebral infarction versus control.

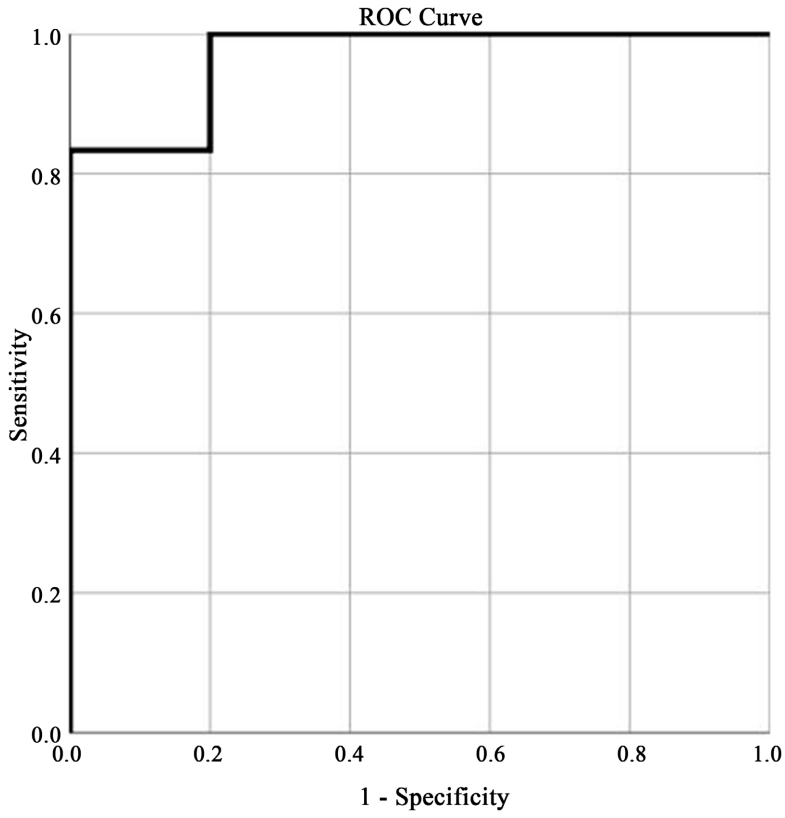

Figure 3. Roc curve of VWF in diagnosis of recurrent cerebral infarction versus control.

Table 6. Correlation coefficient between VWF and ADAMTS13 in 3 studied groups.

	Group (A)	Group (B)	Group (C)
R	0.02	−0.05	0.38
P	0.93 NS	0.85 NS	0.27 NS

No correlation exist between VWF and ADAMTS13 in the 3 groups.

No correlation exists between VWF and ADAMTS13 in 3 groups (**Table 6**).

4. Discussion

Large multimeric plasma glycoprotein called Von Willebrand Factor (VWF) is crucial for initial hemostasis. ADMTS13 and VWF work together to significantly contribute to arterial thrombosis. Platelet adherence to collagen fibres, the formation of atherosclerotic plaques, and platelet aggregation in high shear conditions are all dependent on VWF [2].

VWF increased and ADAMTS13 level reduced in the early stages of acute ischemic infarction. A higher risk of complications and severe neurological damage was indicated by the rise in plasma VWF and FVIII in patients with ischemia infarction [9].

Thin, highly branched fibrin fibres produce fibrin clots that are more stiff, impermeable, and resistant to fibrinolysis [12].

Comparing patients with ischemia infarction to healthy people, relevant studies found that they had lower clot permeability and prothrombotic clot phenotypic characteristics [13].

Additionally, our study revealed that infarction is more common in women (25) than in men (13); Meagha and Louse [14] reported that patient age modified the influence of patient sex in ischaemic infarction and that early in life, the burden of ischaemic infarction is higher in men, but infarction becomes more common and crippling in elderly women.

In addition, this result is consistent with the findings of Kathryn *et al.* [15], who noted that women have a disproportionately high risk of infarction mortality and disability. Additionally, they noted that disparities in infarction risk factors, assessments, treatments, and results are influenced by both biological sex and sociocultural gender. Also concur with Gaignard *et al.* [16], who described how sex hormones affect brain mitochondrial activity as people age and develop neurodegenerative illnesses.

Additionally, our findings are consistent with those of Amiri-Nikpour *et al.* [17] and Mazure and Jones [18], who stated that although the female sex may not independently predict mortality, it is important to recognize that the average female infarction patient will be at a higher risk for death than will her male counterparts, so sex stratification of clinical trial results is crucial in determining whether the risk benefit ratio is sex dependent.

According to Edward *et al.* [19] who reported that CBC is the baseline study that may reveal a cause for the infarction, provide evidence of concurrent illness,

and ensure the absence of thrombocytopenia when considering fibrinolytic therapy, complete blood counts (CBC) are done for all studied groups as far as laboratory investigations go in the current study.

Between the control group and the two study groups, there was no statistically significant change in the total leucocytic count or Hb, according to the current study.

Also, the present study showed significant difference as regards RBCs between the two studied groups and also between acute infarction & control and non-significant differences between chronic infarction group and control.

This result is consistent with the findings of Xu *et al.* [20], who stated that while red blood cells are the most numerous cells in blood, it is not possible to directly assess their contribution to the coagulation process.

According to Martínez-Martínez *et al.* [21], who reported that cerebral thrombosis has a hypercoagulable state prior to the onset of symptoms, the current study found no differences in prothrombin time that were statistically significant. Local hypercoagulability, however, is one of the main causes of acute ischaemic infarction in adults.

Additionally, the study found a substantial difference between the control group and the investigated patients in terms of PT concentration and PTT.

This result is consistent with the findings of Tanaka *et al.* [22], who indicated that mounting evidence suggested that cerebral thrombosis patients have a hypercoagulable state prior to the development of symptoms. Therefore, it is crucial to be able to assess at-risk patients before myocardial infarction begins.

These tests are carried out on plasma since it contains all coagulation factors; nevertheless, in order to better understand the intricate interactions between coagulation factors in whole blood, whole blood samples must be used in the development of in vitro coagulation tests [20].

Except for serum direct bilirubin, which significantly differs between acute cerebral infarction and control in the current study, there were no significant differences between the studied groups in terms of liver and kidney function; this finding is consistent with Antonio *et al.* [23] who reported small changes in bilirubin during the acute phase of infarction, the significance of which is still unclear.

The key distinction in terms of kidney function comes from Chiara *et al.* [24], who reported that ischemic infarction is linked to non-neurological consequences such as kidney and liver injury.

According to Antonio *et al.* [23], changes in bilirubin during ischaemic infarction reflected two phenomena that are both related to inflammation, with a subsequent increase in CRP. Our study found a significant difference between the studied groups and the control group in terms of liver function, kidney function, and C-reactive protein levels.

Also, according to Ormstad *et al.* [25], the substantial independent association between the size of the ischaeic lesion and CRP shows that inflammation over the course of infarction is directly correlated with cerebral injury.

The concentration of ADAMTS13 differed significantly between the control and study groups in the current investigation, indicating that it decreased in the study groups.

This result is consistent with Zhao *et al* findings [26] that ADAMTS13 provides systemic protection against ischemic myocardial and cerebral infarction.

This option is consistent with the findings of Favresse *et al.* [3] who observed that citrated platelet poor plasma is typically used for the ADAMTS13 test to ensure platelet depletion. Estimation and ADAMTS13 are performed on poor plasma rather than serum.

Our selection of ADAMTS13 in cerebral infarction is consistent with the findings of Xin Chen *et al.* [27], who revealed that ADAMTS13 has lately been closely associated with infarction and plays a function in thrombosis. Additionally, it has been observed that ADAMTS13 inhibits platelet-VWF interaction, which limits the development of thrombosis-injured microvenules and controls thrombosis in arterioles [28].

Additionally, our discovery of a low level of ADAMTS13 is consistent with a report by Xin *et al.* [27] that individuals with ischemic infarction have significantly reduced levels of ADAMTS13 in cerebral vascular angiogenesis. Additionally, they noted a strong correlation between ADAMTS13 levels and the occurrence of ischemic infarction. Additionally, the results of Michelle *et al.* [29] showed that people with both the lowest ADAMTS13 and the highest VWF had a higher risk of iscahemic infarction concurs with our discovery of a low ADAMTS13 and high VWF level.

Regarding VWF, there was a significant difference between the study groups and the control group. This finding is consistent with that of Manasa *et al.* [30] that the ADAMTS13 and VWF axis contribute to thrombo inflammation in experimental models and that high VWF levels and low ADAMTS13 levels are linked to an increased risk of ischaemic infarction.

The effectiveness of thrombolytic intervention in cases of acute ischemic infarction is critically dependent on early diagnosis and prompt treatment. Given their significant involvement in a number of thrombotic and inflammatory disorders, VWF and ADAMTS13 axis may also have larger implications than initially thought, including myocardial infarction in addition to ischemic infarction [30].

5. Conclusion

Based on the findings obtained in the present study, we can confirm the protective effect of ADAMTS13 against ischemic reperfusion injury on the brain and its onset, progression, and prognosis. The risk of infarction is strongly correlated with the VWF: ADAMTS13 ratio. A prothrombin condition combined with ADAMTS13 may cause a cerebral infarction, although complete ADAMTS13 deficiency alone does not. Acute cerebral infarction can be predicted with reasonable accuracy by looking at the level of ADAMTS13. Although ADAMTS13

is a weak diagnostic test for recurrent cerebral infarction, it is an effective diagnostic test for acute cerebral infarction. An excellent diagnostic marker for distinguishing between acute and recurrent cerebral infarction is ADAMTS13. In patients with acute and recurrent cerebral infarction, VWF is a highly effective diagnostic tool. In the three groups that were examined, there is no relationship between VWF and ADAMTS13. It is anticipated that ADAMTS13 will emerge as a potential therapeutic option for acute cerebral infarction.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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