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RESEARCH

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Role of Von Willebrand factor level as a biomarker in acute ischemic stroke

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Abstract

Background Von Willebrand factor (VWF) is a large, multimeric glycoprotein that plays a role in thrombus formation; it is also an important mediator of inflammation. Our study aims to determine the association of VWF plasma level and acute ischemic stroke and determine plasma level of VWF in different subtypes of acute ischemic stroke. This case–control study was conducted on 90 subjects: 30 acute ischemic atherosclerotic stroke patients, 30 acute cardioembolic stroke patients and 30 healthy age and sex-matched control subjects. Stroke patients were recruited within the first week of stroke onset with an age range from 18 to 75 years. All subjects underwent complete neurological examination, duplex ultrasonography (U/S), CT brain, routine laboratory work-up and serum level of VWF.

Results VWF serum levels were significantly elevated in patients of acute ischemic stroke, compared to control subjects. Higher plasma levels of VWF were observed in patients with acute ischemic atherosclerotic stroke.

Conclusion Serum level of VWF can be used as a marker for acute ischemic stroke, especially the atherosclerotic subtype.

Keywords Acute ischemic stroke, Stroke biomarker, VWF plasma level

Background

Von Willebrand factor (VWF) is a large multimeric plasma glycoprotein that plays an important role in primary hemostasis. It is synthesized in vascular endothelium and megakaryocytes, then stored in Weibel–Palade bodies of endotheliocytes and granules of platelets or released into the circulation. Upon vascular wall damage, plasma VWF binds to collagen in the exposed subendothelial matrix, and platelet glycoprotein Iba (GPIba) triggers platelet aggregation and thrombus formation [1].

Levels of VWF were significantly elevated in patients with transient ischemic attack (TIA) or ischemic stroke attributed to large artery atherosclerosis, compared with the other stroke subtypes. VWF serves as a useful marker of atherosclerosis and subsequently, a risk marker of stroke [2].

The aim of this work is to evaluate the association of VWF plasma level in subtypes of acute ischemic stroke and correlate its level with the severity of the stroke measured by National Institute of Health Stroke Scale (NIHSS) [3], and functional outcome measured by modified Rankin Scale (mRS) [4].

Methods

This is a case–control study, 90 subjects were recruited from Kasr Al Ainy Hospital ED and were admitted to the Stroke Unit. Patients were subsequently divided into 3 groups: group I, 30 acute ischemic atherosclerotic stroke patients; group II, 30 acute cardioembolic stroke patients; and group III, 30 age and sex-matched normal healthy control subjects. All ischemic stroke patients were recruited within the first week of stroke onset. The

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study was conducted between January 2020 and January 2021.

The G*Power 3.1.9.7 program (Heinrich Heine Universität Düsseldorf) was used to estimate the sample size for our study. For an effect size 0.8, error 0.05 and at a Power of 0.8 a minimum of 27 for each group was determined. In this study 30 subjects were recruited in each group.

Inclusion criteria were as follows: age range 18–75 years, both sexes, acute ischemic stroke patients, within 7 days of symptoms onset, patients with a good temporal window. Exclusion criteria: patients < 18 years and > 75 years, patients with subarachnoid, subdural, extradural, or intracerebral hemorrhage, malignancy, and CNS infection.

Patients' demographics and vascular risk factors including diabetes, hypertension, smoking, and hyperlipidemia were documented. General and neurological examinations including NIHSS [3] were used for assessment of stroke severity and mRS was [4] used for assessment of functional outcome.

Applying extracranial and transcranial neuro-sonological assessments using Philips IU22 duplex machine software, version 2.0.13, USA 2012, carotid artery stenosis was defined according to the criteria set by society of radiologists in ultrasound 2003 [5]. Diagnosis of intracranial stenosis was interpreted according to the internationally published criteria [6]. Intima medial thickness (IMT) above 1 mm at any age is associated with a significantly increased risk of myocardial infarction and/or cerebrovascular disease [7].

Computed tomography (CT) brain (GE multislice 64, 32 detector *2, USA, 2015), routine laboratory investigations include complete blood count (CBC), bleeding profile (prothrombin time, prothrombin concentration and international normalized ratio), kidney functions (urea and creatinine), liver functions (aspartate aminotransferase AST, alanine transaminase ALT, albumin, total and direct bilirubin), electrolytes: serum sodium (Na) and serum potassium (K), serum lipid profile (total cholesterol level, triglycerides, low density lipoprotein LDL and high density lipoprotein HDL), uric acid, fasting blood sugar, postprandial blood sugar, HbA1C.

Serum level of VWF, was measured by enzyme linked immunosorbent assay (ELISA) based on the biotin double antibody sandwich technology using stat fax-2100 device. The reference interval and normal range of VWF was calculated and was determined to be 6–24 ng/dl. The reference range was established in the lab according to CLSI EP28-A3C guideline to define and establish reference intervals in clinical laboratories.

Statistical methods: Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. Data were summarized using median and interquartile range in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Kruskal–Wallis and Mann–Whitney tests [8]. Correlations between quantitative variables were done using spearman correlation coefficient [9]. *P*-values less than 0.05 were considered as statistically significant.

The ethical review board of Cairo University revised and approved the study protocol. All the study participants were treated according to the Helsinki declaration of Biomedical ethics. Written informed consent was obtained from the patients or their caregivers.

Results

Sixty stroke patients and 30 age and sex-matched control subjects were recruited in this study. Patients were subsequently divided into 3 groups: group I, 30 acute ischemic atherosclerotic stroke patients; group II, 30 acute cardioembolic stroke patients; and group III, normal healthy control subjects.

The age of the selected patients ranged from 31–74 years, and age of control subjects ranged from 34–60 years**.** In patients' groups: there were 39 males (65%) and 21 females (35%), while in control subjects there were 20 males (66.7%) and 10 females (33.3%). In group I there were 20 males and 10 females, while in group II there were 19 males and 11 females.

Tables 1 and 2 show the comorbidities and vascular risk factors in patients and control groups. Thirty-five out of 60 patients had a cardiac problem which includes: valvular heart disease, cardiomyopathy (ischemic or non-ischemic) (58.3%), 27 had abnormal ECG (45%) in the form of atrial fibrillation. Thirty-two patients had abnormal echo (53.3%) in the form of

Table 1 Comorbidities and risk factors in patients and control groups

Group				
Patients (60)			Control (30)	
	Number of patients	Percentage	Number of patients	Percentage
HTN	35	58.3	15	50.0
DM	26	43.3	3	10.0
Cardiac	35	58.3	0	0.0
Smoking	37	61.7	15	50.0
Hyperuricemia	12	20.0	2	6.7
Dyslipidemia	34	56.7	5	16.7

HTN: hypertension, DM: diabetes mellitus

Table 2 Risk factor in subgroups of stroke patients and control groups

Risk factor	Group I (30)		Group II (30)		Group III (30)	
	Number of patients	Percentage	Number of patients	Percentage	Number of patients	Percentage
HTN	14	46.6	19	63.33	15	50.0
DM	14	46.6	12	40	3	10.0
Cardiac	6	20	29	96.6	0	0.0
Smoking	19	63.33	18	60	15	50.0
Drug abuse	8	26.66	6	20	0	0.0
Previous stroke	10	33.3	9	30	0	0.0
Hyperuricemia	8	26.66	4	13.33	2	6.7
	22	73.33	26	86.66	28	93.3
Dyslipidemia	22	73.33	12	40	5	16.7
	8	26.66	18	60	25	83.3

HTN: hypertension, DM: diabetes mellitus

Table 3 NIHSS score in subgroups of patients

NIHSS score	Group I (30)		Group II (30)	
	Number	Percentage	Number	Percentage
0–5	6	20	3	10
5–10	12	40	9	30
10–15	8	26.6	13	43.33
15–20	4	13.3	5	16.66

NIHSS: National Institute of Health Stroke Scale

Table 4 mRS score in patients' subgroups

mRS score	Group I (30)		Group II (30)	
	Number	Percentage	Number	Percentage
Favorable outcome (0–2)	10	33.33	7	23.33
Unfavorable outcome (3–6)	20	66.66	23	76.66

mRS: modified Rankin Scale

dilated left atrium, cardiomyopathy, impaired contractility, regional wall motion abnormalities and valvular dysfunction.

Patients' NIHSS ranged from 2 to 19 with a mean of 10.28 ± 4.56 SD. Patients' mRS score ranged from (1 to 5) with mean of 3 ± 0.99 as in Tables 3 and 4.

Forty-eight patients (80%) had anterior circulation stroke, while 12 patients (20%) had posterior circulation stroke. In group I: 23 patients had anterior circulation stroke, 7 patients had posterior circulation stroke, while in group II: 25 patients had anterior circulation stroke, 5 patients had posterior circulation stroke as shown in Table 5.

Among 60 patients, 36 had increased intima media thickness (IMT) on both sides (60%) and 24 patients with normal (IMT) on both sides (40%), compared to 30 control subjects who had normal IMT on both sides, as described in Table 6.

Forty patients had abnormal duplex finding either intracranial or extracranial (66.7%), 20 patients had normal duplex (33.3%). Duplex findings are shown in Tables 7 and 8.

Table 5 Site of infarction in patients' subgroups

		Patients			
		Group I (30)		Group II (30)	
		Number	Percentage	Number	Percentage
Site of infarction	Anterior circulation	23	76.66	25	83.33
	Posterior circulation	7	23.33	5	16.66

Table 6 IMT in patients' subgroups

		Patients			
		Group I (30)		Group II (30)	
		Number	Percentage	Number	Percentage
IMT /cm	Increased	24	80	12	40
	Normal	6	20	18	60

IMT: intima media thickness

Table 7 Transcranial and intracranial duplex findings in patients' groups

		Patients (60)	
		Patients number	Percentage
Extracranial arteries stenosis	None	41	68.3
	Mild	3	5.0
	Moderate	9	15.0
	Severe	7	11.7
Intracranial arteries stenosis	None	15	41.7
	Moderate	13	21.7
	Severe	22	36.7

Table 8 Duplex state in group I and II

		Group I (30)		Group II (30)	
Extracranial arteries stenosis	No	16	53.3%	25	83.3%
	Mild	3	10.0%	0	0.0%
	Moderate	5	16.7%	4	13.3%
	Severe	6	20.0%	1	3.3%
Intracranial arteries stenosis	No	8	26.7%	17	56.7%
	Moderate	10	33.3%	3	10.0%
	Severe	12	40.0%	10	33.3%

Table 9 Comparing VWF plasma levels between patients and control groups

	Patients (60)		Control (30)		*P* value
	Median	IQR	Median	IQR	
VWF	29.05	26.40–61.40	20.45	17.00–24.90	< 0.001***

*** Very highly significant VWF: Von Willebrand factor

It was noticed that higher levels of VWF were present in acute ischemic patients than in control subjects. Such a difference was statistically highly significant (*P* value < 0.001***) as in Table 9 and Fig. 1.

Higher plasma level of VWF was noticed in patients with acute ischemic atherosclerotic stroke (group I) than in patients with acute cardioembolic stroke (group II) with statistical significance. *P* value = 0.025* as in Table 10 and Fig. 2.

We found increased level of VWF in patients with increased intima media thickness (IMT) (49.68 ± 28) compared to patients with normal intima media thickness (IMT) (40.35 ± 21.82 ng/dl), however such difference was not statistically significant, *P* value = 0.386 as described in Table 11 and Fig. 3.

No statistical significance was detected while comparing VWF plasma levels with degree of overall stenosis in patients, *P* value = 0.112 as in Table 12.

Also, no statistical significance was found while comparing VWF plasma levels with degree of stenosis of extracranial or intracranial arteries in patients p value = 0.090, *P* value = 0.316 as in Table 13.

No statistically significant difference was detected when comparing VWF levels in patient with anterior circulation infarction (46.73 ± 27.74 ng/dl) versus posterior circulation infarction patients (42.82 ± 17.42 ng/dl), *P* value = 0.904.

There was no statistically significant comparative between VWF plasma levels and renal function, hepatic function, lipid function, uric acid and HbA1C.

No statistically significant difference in VWF level between males and females with *P* value = 0.768.

No statistically significant relation was observed between VWF plasma level and NIHSS score, mRS score and age in patients' group (*P* value 0.787, 0.411, 0.625), respectively.

Discussion

In the current study, it was observed that VWF plasma levels were significantly higher in patients with acute ischemic stroke within the first week of stroke onset than in serum of control subjects. It can be explained by the role of VWF in platelet adhesion and thrombus formation. VWF is a large, multimeric glycoprotein present in blood plasma endothelium and binds to other proteins, particularly factor VIII, preventing its rapid degradation. It is mediating initial platelet adhesion at sites of vascular injury. Although this is a prerequisite for normal hemostasis, adhesion of platelets is also the first step in thrombosis and an important mediator of inflammation [10]. Similar to our results, Menih et al. [11], found that elevated level of von Willebrand Factor (VWF) is associated with increased risk for coronary heart disease and ischemic stroke. Barakzie et al. [12], also found that VWF is associated with risk of ischemic stroke, stroke severity, and clinical outcome. Hanson et al. [13] found that VWF levels are increased in patients with ischemic stroke

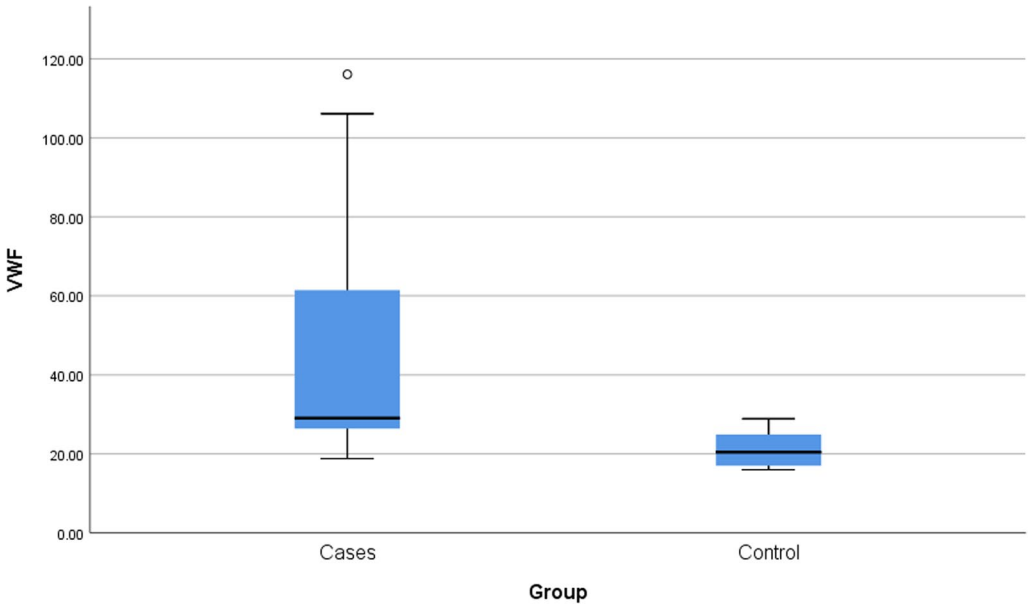

Fig. 1 VWF levels (ng/dl) in patients and control subjects

Table 10 Comparing VWF plasma levels between patients' subgroups

	Patient subgroups				
	Group I (30)		Group II (30)		
	Median	IQR	Median	IQR	*P* value
VWF	57.90	27.10–64.20	27.20	25.60–57.50	0.025*

Significant* VWF: Von Willebrand factor

compared to control subjects, it was explained by role of VWF in acute phase of ischemic stroke and prothrombotic effects of VWF that play a role in atherosclerosis/inflammation or endothelial damage [13, 14].

VWF is predominantly released from endothelial cells. Damage to the endothelium in atherosclerosis increases the release of VWF, which can lead to a sudden thrombus formation in the arteries [11]. The VWF is a major

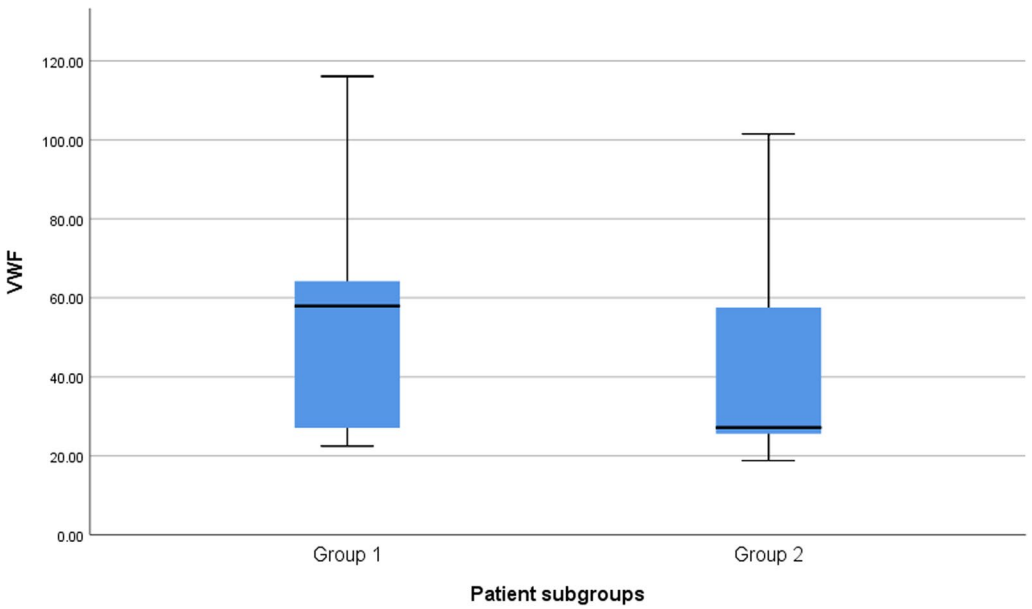

Fig. 2 VWF plasma levels (ng/dl) in patients' subgroups

Table 11 Comparative between VWF levels and IMT

Number of patients (60)	IMT/CM				*P* value
	Normal		Abnormal		
	Median	IQR	Median	IQR	
VWF	28.00	26.35–59.90	43.60	26.60–62.30	0.386

VWF: Von Willebrand factor, IMT: intima medial thickness, CM: centimeter

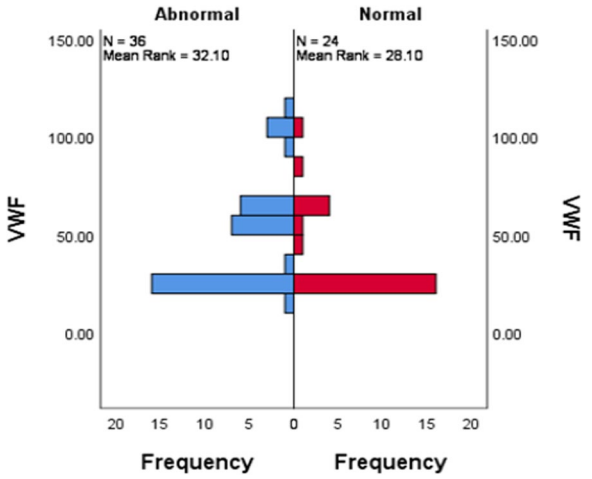

Fig. 3 Comparative between VWF levels (ng/dl) and IMT in patients using independent-samples Mann–Whitney U test

Table 12 Comparative between VWF levels and overall degree of stenosis in duplex

Number of patients (60)		VWF		*P* value
		Median	IQR	
Degree of stenosis	No stenosis	28.80	26.40–58.60	0.112
	Mild	106.10	106.10–106.10	
	Moderate	27.30	24.20–60.50	
	Severe	57.20	26.80–64.70	

VWF: Von Willebrand factor

factor for the accumulation and activation of platelets in stenotic arteries, which can lead to acute thrombotic occlusion, and it has a dual role, participating in normal hemostasis as well as in the pathological process of thrombus formation in arteries [11].

In our study higher plasma levels of VWF were more significantly associated with acute ischemic atherosclerotic stroke patients, than in patients with acute cardioembolic stroke (P value = 0.025). Our results were similar to the studies performed by Sonneveld et al., and Buchtele et al., where VWF plasma levels were significantly raised in patients of acute ischemic stroke. A

Table 13 Comparative between VWF levels and degree of stenosis of extracranial and intracranial arteries in patients

Number of patients (60)		VWF		*P* value
		Median	IQR	
Extracranial arteries stenosis	No	27.80	26.40–57.50	0.090
	Mild	65.30	59.70–106.10	
	Moderate	60.50	25.40–101.50	
	Severe	58.30	26.70–64.20	
Intracranial arteries stenosis	No	29.30	26.40–60.50	0.316
	Moderate	27.30	24.30–59.70	
	Severe	43.30	26.80–64.20	

VWF: Von Willebrand factor

strong positive association was detected between the extent of atherosclerosis, and VWF levels [15, 16]. Kraft et al. [17] noticed that subjects with carotid plaques have elevated VWF plasma levels.

It could be explained by association of VWF level in the acute phase after ischemic stroke and its association with inflammation and thrombo-inflammation. The term "thrombo-inflammation" describes the interaction of thrombotic (for example, coagulation factors, platelets) and inflammatory (for example, immune cells) circuits that occurs at the ischemic neurovascular unit and has been identified as key mechanism of stroke occurrence and propagation.

On the other hand, Maida et al. [18], observed higher levels of VWF in patients with cardioembolic acute ischemic stroke compared to other stroke subtypes. Hanson et al. [13] found that levels of VWF in the acute phase of both cardioembolic and atherosclerotic stroke were significantly higher compared to the small vessel disease subtype of stroke.

In our study we found no significant association between VWF plasma levels and the degree of stenosis of intracranial or extracranial arteries in patients with acute ischemic stroke. On the contrary Murphy et al. [19], found that VWF antigen expression is enhanced in symptomatic versus asymptomatic carotid stenosis patients. Also, Kinsella et al. [20], found that endothelial activation is enhanced in symptomatic versus asymptomatic carotid stenosis patients. VWF levels increase in early symptomatic versus asymptomatic carotid stenosis [21, 22].

In the current study, NIHSS and mRS scores were not associated with higher plasma levels of VWF, there was no statistical significance for this. However, it may be related to a limited number of patients. Meanwhile, Menih et al. [11], found that patients with high NIHSS score on admission had significantly higher levels of VWF as a predictor for the severity of stroke. Also, patients

with high mRS score as a predictor of unfavorable outcome at discharge (mRS ≥ 3) had significantly increased levels of VWF on admission.

Sonneveld et al. [15], stated that VWF Ag levels were significantly correlated with the NIHSS score at admission and with functional outcome of the patients, as determined by mRS at discharge. Patients with an unfavorable outcome (mRS > 2) had significantly higher VWF Ag levels compared with patients with a favorable outcome.

Conclusion

The current study concludes that, VWF can be a good biomarker for ischemic stroke, especially atherosclerotic type of ischemic stroke. Limitations of this study include small sample size and to follow up patients for a longer period of time to assess long-term functional outcome.

Abbreviations

ALT	Alanine transaminase
AST	Aspartate transaminase
CBC	Complete blood count
CNS	Central nervous system
CT	Computed tomography
DM	Diabetes mellitus
ED	Emergency Department
ELISA	Enzyme linked immunosorbent assay
GPIba	Glycoprotein Iba
HDL	High density lipoprotein
HTN	Hypertension
IMT	Intima medial thickness
INR	International normalized ratio
IS	Ischemic stroke
LDL	Low density lipoprotein
mRS	Modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
RWMA	Regional wall motion abnormalities
SD	Standard deviation
TG	Triglycerides
TIA	Transient ischemic attack
US	Ultrasonography
VEGF	Vascular endothelial growth factor
VWF	Von Willebrand factor

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Author contributions

A.S.S shared in the patient collection, supervision and revised the manuscript. M.M.E was the idea founder, shared in the patient collection, and the supervisor in all the steps. D.M.L shared in the patient collection and supervision. M.S.H shared in the patient collection and supervision. N.S.W shared in the patient collection, wrote, revised the manuscript and she is the submitting and corresponding author. A.M.A shared in the patient collection and supervision. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The Research Ethics committee (REC) faculty of medicine, Cairo University has reviewed and approved this study in 27-2-2020. Informed written consent was obtained from each participant or their relatives if they were unable to give the consent owing to their medical condition. All methods were carried out in accordance with relevant guidelines and Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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